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Foot ulceration in diabetes mellitus : method of foot pressure measurements and neuro-vascular responses.

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FOOT ULCERATION IN DIABETES MELLITUS:

Methods Of Foot Pressure Measurement

And Neuro-Vascular Responses

by Daniela Luminita Pitei

A thesis submitted for the degree of

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Abstract of the thesis

The main purpose of this thesis was to investigate fundamental mechanisms of ulcer formation by measurement of plantar pressures in diabetic neuropathic patients, who develop plantar ulcers, compared to diabetic patients with ischaemia as well as neuropathy, who in sharp contrast, do not normally develop plantar ulcers.

A methodology has been developed for accurate and reproducible measurement of in-shoe foot pressures using F-Scan technology. Cyclic and sustained loading using an Instron machine were applied in laboratory conditions to investigate time-dependent behaviour of F-Scan insole and procedures for optimal calibration and use were suggested. Clinical validation of the methodology was performed using reliability, variability and reproducibility tests and from these, specific recommendations were derived for the use of F-Scan technique in the clinic.

This technique showed that in-shoe plantar pressures were considerably elevated in neuro-ischaemic feet to an even greater extent than in purely neuropathic feet. However the pattern of pressure loading in neuro-ischaemic feet was no different from controls, whereas those with pure neuropathy had a variable pressure loading during walking.

Factors which affect foot pressures and methods of reducing them were also studied. The reduction in pressure following callus removal was measured, followed by an assessment of pressure rise, as callus reforms. A new type of individually moulded (ethyl-vinyl-acetate) insert was shown to reduce pressures substantially, especially when it has bedded-in. Trainers also had an important, although lesser effect, sometimes sufficient for routine use and still preferable to unfitted High Street shoes, with considerable saving in cost.

Another factor in the evolution of foot ulcer might be abnormal microvascular responses. Vasodilatation was induced by iontophoresis of acetylcholine (endothelium-dependent vasodilator) and sodium nitroprusside (SNP - direct smooth muscle relaxant). Responses to acetylcholine were impaired in all diabetic patients, whereas responses to SNP were specifically reduced in presence of neuropathy. This new finding could be important in pathogenesis of foot abnormalities in diabetes.

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CONTENTS

LIST OF TABLES

in Chapter 1. DIABETIC FOOT COMPLICATIONS

in Chapter 3. FOOT PRESSURES MEASUREMENT

in subchapter 3.4 Validation of a clinical methodology for in-shoe pressure measurement using F-Scan system

in Chapter 4. FOOT PRESSURES ASSESSMENT IN NEURO-ISCHAEMIC DIABETIC PATIENTS VERSUS NEUROPATHIC PATIENTS

in Chapter 5. THE EFFECT OF REGULAR CALLUS REMOVAL ON FOOT PRESSURES

5.1 Clinical and neuropathy details of patients

5.2 Comparisons between the four groups of patients who had chiropodial removal of callus.

in Chapter 6. THE EFFECT OF FITTED SHOEWEAR ON FOOT PRESSURES

6.1 Clinical details of patients

6.2 Peak pressures in prescription shoes versus patient's own shoes.

6.3 Peak pressures in standard trainers versus patient's own shoes.

6.4 Peak pressures in new prescription shoes versus standard trainers.

6.5 Peak pressures followed-up in newly fitted versus worn-in prescription shoes with EVA inserts

in Chapter 7. MICROCIRCULATORY FACTORS AND THEIR ROLE IN THE PATHOGENESIS OF THE DIABETIC FOOT

in subchapter 7.2 The role of microvascular function abnormalities in the pathogenesis of foot ulceration

7.2.1 The microvascular haemodynamics in the diabetic foot

7.3.1 Effect of neuropathy on foot microcirculation

7.4.1 Human NOS isoforms: function, chromosomal and tissue localisation

7.4.2 Factors involved in vasomotricity and vascular cell growth

in subchapter 7.8 Endothelium-dependent and endothelium-independent responses in diabetic patients with peripheral neuropathy

7.8.1 Clinical details of all subjects

7.8.2 Clinical details of the NIDDM patients in which neuro-vascular responses were measured

7.8.3 Basal blood flow and vasodilatatory responses to acetylcholine and SNP iontophoresis in NIDDM patients with and without neuropathy compared to non-diabetic controls and expressed as geometric mean±anti-logged SD.

7.8.4 Vasodilatatory responses to acetylcholine and sodium nitroprusside iontophoresis in all neuropathic patients and non-neuropathic diabetic patients compared to non-diabetic controls and expressed as Mean ± SEM.

in subchapter 7.9 Endothelium-dependent and endothelium-independent responses in non-diabetic patients with peripheral unilateral nerve damage

7.9.1 Clinical details of non-diabetic patients with unilateral nerve damage.

7.9.2 Individual neurophysiological characteristics in 'control' limbs versus 'neuropathic' limbs in non-diabetic patients.

7.9.3 Neuropathy details of the 'control' limb versus the 'neuropathic' limb in non-diabetic patients with unilateral nerve damage

7.9.4 Vasodilatatory responses to iontophoresis of acetylcholine and SNP in 'control' limbs versus 'neuropathic' limbs in non-diabetic patients

7.9.5 Comparisons of vasodilatatory responses to acetylcholine and sodium nitroprusside iontophoresis in neuropathic diabetic patients versus 'neuropathic' limbs in non-diabetic patients with peripheral unilateral neuropathy and control subjects versus 'control' limbs in non-diabetic patients with peripheral unilateral neuropathy

LIST OF FIGURES

in Chapter 1. DIABETIC FOOT COMPLICATIONS

in Chapter 3. FOOT PRESSURES MEASUREMENT

in subchapter 3.2 F-Scan - a new method of foot pressures measurement

in subchapter 3.3 Validation of F-Scan methodology in laboratory conditions.

Time-dependent behaviour of the F-Scan plantar pressure measurement insole

in subchapter 3.4 Validation of a clinical methodology for in-shoe pressure measurement using F-Scan system

3.4.1 Reliability of the insole in consecutive runs.

3.4.2 Life-time of an insole. Creasing and drop-out of the insole during un-consecutive runs.

in Chapter 4. FOOT PRESSURES ASSESSMENT IN NEURO-ISCHAEMIC DIABETIC PATIENTS VERSUS NEUROPATHIC PATIENTS

4.0 Peak plantar pressures analysed under the four main areas of the foot on a F-Scan recording

4.1 Graphic comparison of the mean peak plantar pressures measured in the four groups: non-diabetic and diabetic controls, neuropathic and neuro-ischaemic patients.

4.2 Graphic comparison of the highest peak plantar pressures measured in the four groups: non-diabetic and diabetic controls, neuropathic and neuro-ischaemic patients.

4.3 Graphic comparison of the maximum plantar pressures measured in the four groups: non-diabetic and diabetic controls, neuropathic and neuro-ischaemic patients.

4.4 Interactions for run by step in control and diabetic control groups.

4.5 Interactions for run by step in neuropathic group

4.6 Interactions for run by step in neuro-ischaemic group.

in Chapter 5. THE EFFECT OF REGULAR CALLUS REMOVAL ON FOOT PRESSURES

5.1 Peak plantar pressures who received chiropody treatment for the very first time.

5.2 Peak plantar pressures who received chiropody treatment at 6-8 weeks interval

in Chapter 6. THE EFFECT OF FITTED SHOEWEAR ON FOOT PRESSURES

in Chapter 7. MICROCIRCULATORY FACTORS AND THEIR ROLE IN THE PATHOGENESIS OF THE DIABETIC FOOT

7.4.1 NO synthesis in the endothelium and actions on the smooth muscle

7.4.2 Vasoactive effects of neurotransmitters

in subchapter 7.8 Endothelium-dependent and endothelium-independent responses in diabetic patients with peripheral neuropathy

7.8.1 Laser Doppler blood flow measurements (trace)

7.8.2 Laser Doppler measurements of vasodilatatory responses to acetylcholine iontophoresis in neuropathic patients versus diabetic and non-diabetic controls.

7.8.3 Ratio between the peak blood flow after, and basal blood flow before, acetylcholine iontophoresis in neuropathic patients versus diabetic and non-diabetic controls.

7.8.4 Laser Doppler measurements of vasodilatatory responses to sodium nitroprusside iontophoresis in neuropathic patients versus diabetic and non-diabetic controls.

7.8.5 Ratio between the peak blood flow after, and basal blood flow before, sodium nitroprusside iontophoresis in neuropathic patients versus diabetic and non-diabetic controls.

7.8.6 Comparison of the vasodilatatory responses to acetylcholine and sodium nitroprusside iontophoresis in the neuropathic group

in subchapter 7.9 Endothelium-dependent and endothelium-independent responses in non-diabetic patients with peripheral unilateral nerve damage

7.9.1 Laser Doppler measurements and ratio of vasodilatatory responses to acetylcholine iontophoresis in non-diabetic patients with unilateral nerve damage.

7.9.2 Laser Doppler measurements and ratio of vasodilatatory responses to sodium nitroprusside iontophoresis in non-diabetic patients with unilateral nerve damage.

Chapter 1. DIABETIC FOOT COMPLICATIONS

1.1 Introduction

The diabetic foot is one of the most significant complication of diabetes mellitus (**Frykberg, 1991**). Foot problems have a high incidence in patients with diabetes: 60 000 major lower extremity amputations are performed annually on diabetic patients in the USA only, of which 84% are a result of foot ulcers (**Levin et al. 1993**).

In the UK more hospital beds are occupied by patients with diabetes who have foot problems than all other complications of diabetes combined (**Malins, 1968**). Diabetic foot ulcers are estimated to occur in 15% of all diabetic patients (110 million in the world) during their lifetime (**Reiber 1996**). In Britain the prevalence of foot ulceration has been estimated between 5.3% to 7.4% (**Veves et al 1992**). The associated annual cost to the National Health Service for the diabetic foot inpatient care has been conservatively estimated to be £223.4 million (**Laing et al, 1991**). Treatments that reduce hospital stays by managing these lesions on an out-patient basis or prevent them occurring would be preferred. Recently the St. Vincent Declaration, which has been made in conjunction with WHO, aims to reduce the amputation rate by 50%.

Definition

The diabetic foot can be defined in two categories:

1. the purely neuropathic foot, characterised by the presence of neuropathy, but without ischaemia.
2. the neuro-ischaemic foot, characterised by both diabetic neuropathy and peripheral vascular disease.

The correct diagnosis of each type is important, as each has characteristic complications, such as different types of ulcer, requiring specific treatment.

Assessing the vascular status in addition to the neurological status would help in diagnosing the type of diabetic foot. Thus the neuropathic foot is diagnosed when neuropathy is present but foot pulses are palpable and the ankle-brachial pressure index is > 1, whereas the neuro-ischaemic foot is diagnosed when neuropathy is present but foot pulses are impalpable and/or Doppler index is < 0.8.

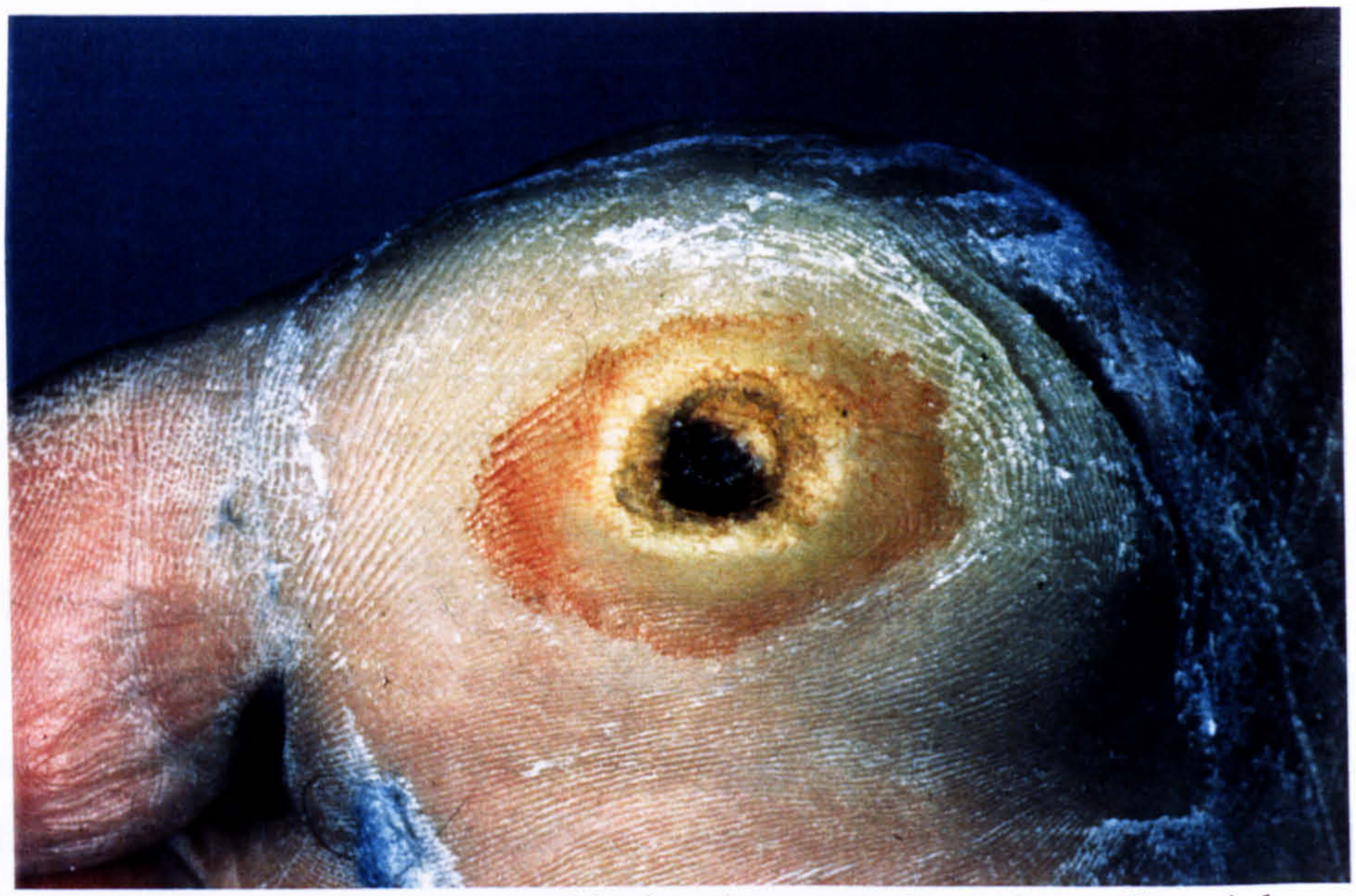

Figure 1.1 The diabetic neuropathic foot is warm, dry and usually painless, with palpable pulses and abundant callus formation. Its most important and frequent complication is the neuropathic ulcer commonly occurring on the plantar surface.

Fig 1.2 The diabetic neuro-ischaemic foot is characterised by neuro-ischaemic ulceration on the margins of the foot, and by rest pain and gangrene in the presence of peripheral neuropathy.

There has been little research into causes of neuro-ischaemic ulceration, although considerable attention has been paid to the neuropathic ulcer. This introduction will review the literature on risk factors associated with ulcer formation in diabetes, focusing on the two types of diabetic foot:

- the diabetic neuropathic foot
- the diabetic neuro-ischaemic foot.

1.2 The diabetic neuropathic foot

The earliest description of a diabetic neuropathic plantar ulcer was made by **Mott** in 1818 (cited in **Croft et al., 1982**). These ulcers were recognised as a complication of diabetes before 1870 (**Faris, 1991**), but it was not until the end of the 19th Century that hypotheses concerning their aetiology were published. **Treves (1884)** believed diminished "nutrition[1] of certain parts" of the foot; "dulled" sensation of the sole; and the effects of "pressure upon the skin" were "the chief factors in the production of perforating ulcers". He thought "disturbance of nutrition" was the most important aetiological factor after observing plantar ulcers in patients without "perverted sensation in the limb" and "nothing peculiar in the pressure to which the part" was subjected. **Pryce (1887)** believed "locomotor ataxy" (motor neuropathy) and "peripheral neuritis" (sensory neuropathy) to be causative factors in ulceration; and noted that the previously ulcerated feet of patients with diabetes sometimes showed a "glossy skin" - a suggestion of autonomic neuropathy.
Therefore a variety of factors were thought to play a role in the aetiology of foot ulceration.

Risk factors for foot ulceration in diabetes mellitus

1.2.1 Diabetic peripheral neuropathy

Ulcers on the plantar surface of the foot are typically found in diabetic patients with peripheral neuropathy. Sensory loss plays a vital role in predisposing to the development of these lesions (**Masson et al., 1989**). Peripheral neuropathy is a complication of long-term diabetes mellitus that is apparently related to the glycaemic control and duration of the disease (**Pirart, 1977**). A strong correlation with age and a predominance among male patients has also been found (**Greene et al., 1990**).

Somatic sensorimotor neuropathy is the most common and recognisable type of nerve disorder in patients with diabetic foot (**Frykberg, 1991**). Sensory involvement begins *distally* in the toes and progresses *proximally* (**Dyck, 1987**) leading to loss of pain and thermal sensation, impaired or absent ankle reflexes and reduced vibration perception and light touch sensation. The inability to perceive pain predisposes the foot to injury from

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[1] "nutrition" in this context most likely refers to a reduced blood supply, with a subsequently reduced supply of oxygen and nutrients, such as glucose, to the tissues.

burns, and mechanical injury e.g. from treading on sharp objects or the repeated forces of gait. Denervation of the motor fibres to the extensor digitorum brevis, lumbrical and interosseous muscles can cause the metatarsophalangeal joints to become hyperextended and the interphalangeal joints flexed. Subsequent claw-toe deformities lead to anterior displacement of the sub-metatarsal fat cushions and prominent metatarsal heads (**Bojsen-Moller, 1979**). Atrophy of plantar adipose tissue of the heel and the sub-metatarsal fat cushions may also lead to bony prominence (**Gooding et al., 1986, Jahss et al., 1992**). However pure sensorimotor neuropathy is unusual (**LeQuesne et al., 1991**): a close association with autonomic neuropathy exists (**Edmonds, 1987**).

Autonomic neuropathy in the foot is characterised by impaired sweating resulting sometimes in dry, cracked skin which acts as a portal of entry for sepsis, and vasomotor denervation (**Archer et al., 1984**; **Corbin et al., 1987**; **Irwin et al., 1988**). The latter causes a huge increase in peripheral blood flow, opening of arteriovenous shunts, and can lead to arterial medial wall degeneration with calcification (**Watkins, 1990**). A warm foot associated with a high blood flow which may be more than five times normal are characteristic features of the neuropathic foot. These major haemodynamic changes are at least in part responsible for oedema in the neuropathic foot, occasionally of considerable severity. Increase in bone blood flow also occurs and may cause osteopenia, and this could underlay the development of the destructive bony changes of Charcot joints.

Table 1.1 Possible consequences of vasomotor denervation in the neuropathic foot

Arteriovenous shunting and increased peripheral blood flow	Oedema
Increased bone blood flow	Osteopenia and Charcot joint
Medial calcification	Rigid arteries and high ankle/ brachial systolic pressure index

Sympathetic denervation of the arteries to the foot also leads to increased vascular rigidity and medial calcification which is also commoner after lumbar sympathectomy (**Edmonds et al., 1986**). While there is no evidence that reduced blood flow results from this, Doppler examination of the foot circulation may give misleading results because of the incompressibility of the arteries.

Methods for diagnosis and assessment of diabetic neuropathy

Clinical neurological tests

Neurological status can be simply assessed in the clinic by detecting pain sensation to pinprick, light touch sensation to cotton wool and vibration using a 128 cps tuning fork starting distally from the foot up-wards to confirm a symmetrical stocking distribution of peripheral neuropathy. Absence of ankle jerks is evidence of peripheral neuropathy, although knee jerks are retained until surprisingly late. A dry skin with marked fissuring can be suggestive of a sweating autonomic deficit. Two investigations used in the clinic: vibrometry and nylon filaments are most useful to detect the patients susceptible to foot ulceration.

Vibration perception threshold (VPT)

This can be measured using a hand-held biothesiometer (Bio-medical Instrument Company, 15764 Munn Road, Newbury, Ohio 44065, USA). The vibration threshold increases with age, and values must always be compared with age-adjusted nomograms. A threshold for ulceration has been defined by Young et al.. (**Young et al., 1994**) who found that a VPT>25Volts is a good predictor for the risk of ulcer formation. Thus the measurement of the vibratory perception threshold is clinically useful in identifying those diabetic patients at high risk of foot ulceration (**Boulton et al., 1986**).

Other tests of nerve function

VPT is a measure of large fibre function, whereas other tests, such as thermal perception threshold (TPT) for cold and warm have been used to assess small nerve fibre function (**Sosenko et al., 1988**). However this is a less simple test than the VPT and more time consuming, being therefore recommended more for research purposes than for common use in the clinic. The same applies to motor and sensory nerve conduction velocity tests, which are probably the most exact diagnostic tests, but they require special equipment which is not always available in the clinic.

An attempt was made to develop a device, the Neurometer, which would be a simple and comprehensive way of assessing peripheral nerve function (**Masson et al., 1989**) by measurement of current perception threshold. Although the Neurometer

showed a degree of neuroselectivity, it also showed a large variability like all subjective sensory tests (**Pitei et al., 1994**). The motor and sensory conduction velocity tests are more precise measurements, but they are mainly used for research purposes and less so in the Foot Clinic.

Semmes-Weinstein monofilaments

The Semmes-Weinstein monofilaments (Hansen's Disease Foundation Inc., Carville, Louisiana, USA), which test the threshold to pressure sensation are much easier and quicker to use in the clinic. The nylon filament is applied to the foot until it buckles, when the patient should be able to detect its presence. Buckling of the 5.07 monofilament occurs at 10g of linear pressure and is the limit used to detect protective pain sensation. If the patient does not detect the filament, then protective pain sensation is lost. A study comparing Semmes-Weinstein monofilaments and VPT (**Kumar et al. 1991**) in 182 subjects attending a national patients conference showed a good correlation between the two measures. The filaments were more sensitive (100%) but less specific (77.7%) in identifying patients who had foot ulcers compared to biothesiometry which was less sensitive (78.6%) but more specific (93.4%). In another study the accuracy of sensory-threshold measurements, VPT and TPT, for detecting diabetic foot ulcer patients was compared with that of cutaneous pressure perception-threshold in 314 non-insulin-dependent diabetic patients, of whom 91 had either a current foot ulcer or a history of foot ulceration. Pressure thresholds were highly accurate for identifying foot ulcer patients (**Sosenko et al., 1990**). The filaments are therefore reliable and may be superior to VPT and TPT in screening for patients at risk of foot ulceration since sensitivity is the more important parameter. In addition, they are inexpensive and are simple and easy to use as a screening device for identifying diabetic patients at risk of foot ulceration in the diabetic clinic or in general practice.

Conclusion

Diabetic peripheral neuropathy is an essential factor in the pathogenesis of diabetic foot ulceration. Its diagnosis can be made by clinical neurological and electrophysiological tests, of which vibration perception threshold and Semmes-Weinstein monofilaments are most suitable in the clinic for screening patients at risk of foot ulceration.

1.2.2.Epidemiological risk factors: History of foot ulceration, social status and race

Previous foot ulcer and/or amputation have been shown to increase the ulceration/ amputation risk **(Reiber, 1996)**, as well as a poor social situation especially if patients are elderly and live alone **(Boulton, 1996).** Ethnic differences in the incidence of lower extremity amputations secondary to diabetes have been demonstrated in the UK in Caucasians patients with a 14.2/10000 rate of amputation versus a 3.4/10000 rate in Asian patients **(Gujral et al., 1993)**, who tend to be less likely to develop ulceration possibly related to their joint hypermobility and /or cultural trends in daily foot care **(Toledano et al., 1994)**. An US study assessing the incidence of lower extremity amputations in Pima Indians with NIDDM has found their overall amputation rate to be 24.1/10000 person-years versus 6.5/10000 person-years for the general US diabetic population **(Nelson et al., 1988)**, whereas racial differences have been also demonstrated in black subjects, who tend to have increased subtalar joint mobility and lower foot pressures than the white ones **(Veves et al., 1995)** with effect on their risk of ulceration.

1.2.3 Diabetic microvascular disease

In the diabetic neuropathic foot histological evidence of microangiopathic changes can also be detected at the skin level **(Faris et al., 1991)** and abnormalities in skin local reflexes have been demonstrated by Tooke et al. **(Tooke et al., 1996)** as part of the microangiopathy associated with the diabetic foot and its ulceration. Physiological studies have been carried out in this thesis to explore this risk factor for ulceration and a summary of the relevant literature on this topic is described in the Chapter 7.

1.2.4 Diabetes duration and long-term complications

Diabetes microvascular complications, duration, and control have been shown to be independent predictors for amputation **(Selby et al., 1995)** in diabetic foot patients. Retinopathy has been associated with increased amputation risk **(Reiber et al., 1992).** Risk factors for foot ulceration in diabetic nephropathy are both ischaemia due to associated macrovascular disease, and neuropathy **(Fernando et al., 1991).** In patients with visual and renal impairment, as often found in those with renal transplant, the majority of foot lesions, both in soft tissue and bone, were related to neuropathy **(Foster et al., 1995)**.

1.2.5 Diabetes control

Glycated haemoglobin has been found to be higher in patients with ulcers than in those without (**Croft et al., 1982**). Furthermore the DCCT (Diabetes Control and Complications Trial) established that patients who maintained lower levels of glycated haemoglobin have developed in time less diabetic complications including neuropathy **(DCCT Study Group 1993)**, which has been shown previously to be associated with an increased risk of foot ulceration **(Fernando et al., 1991).** In diabetes an non-enzymatic glycation by which glucose molecules attach to structural proteins takes place leading to alterations in the physical properties of the protein. Therefore poor glycaemic control may be also associated with detrimental connective tissue changes **(Yue et al., 1983)**.

1.2.6 Soft tissue abnormalities

Nonenzymatic glycosylation of collagen (**Schnider and Kohn, 1980**) and keratin **(Delbridge et al., 1983**) has been related to poor diabetic control, which is significant in that glycosylation of collagen produces an increase in intermolecular crosslinking making the skin and subcutaneous tissues rigid and inflexible **(Hamlin et al., 1975**). It is thought glycosylation produces a similar structural change in keratin **(Delbridge et al., 1985**). glycation of keratin may induce thickening of the skin, which becomes less elastic and more vulnerable to injury. Glycosylated keratin may also contribute to the build up of keratin and excessive callus formation, at the sites of weight-bearing which precedes and accompany ulceration. This changes in the properties of connective tissue may increase its vulnerability to high forces developed during gait between the different tissues of the foot, and between foot and ground. This may facilitate tissue breakdown, with formation of cavities and eventually ulcers. It has been hypothesised that rigidity of the skin and subcutaneous tissues and the build up of glycosylated keratin, callus, on the plantar surface in response to pressure, predisposes to ulceration through inadequate pressure distribution during walking **(Frykberg, 1991)**.

Conclusion

Risk factors for ulceration, such as soft tissue abnormalities, diabetes duration, control and microvascular complications, are linked with the presence of diabetes per se, whereas epidemiological factors such as: social status, race and history of previous ulceration have been also shown to increase the ulceration risk.

Despite the presence of predisposing factors such as neuropathy, a patient "at risk" may live for many years without developing an ulcer due to the avoidance of specific precipitating factors; for example, localised high pressure, by applying a high force on a small area, can lead to ulceration by disruption of tissue, such as stepping on a pin. Similarly, repeated mechanical trauma due to forces/pressures developed under the foot during walking could cause ulceration.

1.2.7 Direct/extrinsic mechanical factors implicated in ulcer formation in the neuropathic foot

Extrinsic mechanical factors are common in the foot with neuropathy. They occur mainly when patients with insensitive feet walk barefoot and step without noticing on sharp objects such as stones, pins or when those are inside their shoes, such as protuberant nails.

Chemical injuries occur when using keratolytic agents, such as 'corn plasters', which contain concentrated salicylic acid and may cause liquefaction of the tissue, sepsis and necrosis.

Thermal injuries, for example burns can lead to blisters which subsequently can become infected. Hot water bottle burns are the most frequent cause, also bathing in excessively hot water, or walking barefoot on hot sand during seaside holidays or keeping their feet too close to an open fire or resting on a radiator can lead to foot lesions.

1.2.8 Biomechanical/intrinsic factors implicated in ulcer formation in the neuropathic foot

Most commonly foot ulceration occurs due to abnormalities in the intrinsic biomechanical factors active during gait. Ulcers on the plantar surface of the foot appear to occur at sites of high normal (vertical) pressure **(Ctercteko et al., 1981)**, although a shear component which acts not only at the shoe upper-foot interface, but also in the

depth of the soft tissues of the foot can not be excluded. Moreover repeated applications of 'normal' pressures or shear stresses during activities of daily life **(Brand et al., 1988)** may lead to ulceration in an insensitive foot. When the total force, which is normally distributed on the whole plantar area, is concentrated on small areas such as prominent metatarsal heads in patients with neuropathy, this can increase the pressures dramatically. Therefore the plantar pressures would determine the amount of damage to the foot tissues and be implicated in the ulceration process. Hence the importance of measuring plantar pressures in the diabetic foot with neuropathy.

1.2.9 Foot pressures

Early foot pressure studies have shown that neuropathic feet with previous ulceration had abnormally high pressures at the ulcer site suggesting a correspondence between sites of high plantar pressure and ulceration. They also recommended the measurement of foot pressures as a predictive tool by determining specific areas under the foot that are prone to ulceration **(Boulton et al., 1983)**.

Attempts to determine a pressure threshold for ulceration have been made previously to allow an early identification of elevated stress and a timely therapeutic intervention, such as callus removal and footwear prescription, which can prevent many plantar lesions.

Studies using pedobarography have confirmed that vulnerable areas of the neuropathic foot are those where pressure exceeds 10 kg/cm2 **(Boulton et al., 1987)**. Later Veves et al.. **(Veves et al., 1992)** have reported that all of their ulcer patients had barefoot plantar pressures greater than 11.2 kg/cm2 (equivalent to 1.1 MPa).

In-shoe pressure measurements are considered to give more information about the risk to ulceration, as they measure the forces developed in real life-conditions at the shoe-foot interface. Nevertheless no in-shoe threshold for ulceration has been defined yet **(Hsi et al., 1993)**. However a variety of commercially available systems (see Chapter 3) for plantar pressure measurement are in clinical use at major diagnostic centres and different systems for measuring pressure distribution yield different results on the same patient **(Cavanagh and Ulbrecht, 1991)**, so that results of one study cannot be easily extrapolated to another situation. This highlights the need for an overall understanding of clinical findings from plantar pressure studies.

Clinical findings from plantar pressure studies

In foot pressure studies, diabetic patients have been the most extensively studied patient group. The apices of the toes and the plantar aspects of the first and third metatarsal heads are the most common sites of plantar ulceration in patients with diabetes (**Holstein et al., 1976**; **Ctercteko et al., 1981**; **Edmonds et al., 1986**; **Veves et al., 1992**). As a result, the forefoot has been the main area of interest in diabetic plantar stress studies.

Barefoot measurements

The supposition that plantar ulcers develop at sites of abnormally high pressure has so far been supported by one prospective study. In the period of follow-up of eighty-six patients, **Veves et al.. (1992)** noted that twenty-one plantar ulcers had developed; eight of which were at sites of abnormally high peak pressures (>12.3 kg/cm2) detected at the initial assessment.

Several retrospective studies have found elevated peak pressures to be coincident with the sites of previous ulceration, and significantly higher plantar pressures in patients with neuropathy and healed plantar ulcers, compared to patients with neuropathy and no history of ulceration (**Barrett, 1973**; **Stokes et al., 1975**; **Ctercteko et al., 1981**; **Boulton et al., 1983**; **Duckworth et al., 1985**; **Cavanagh et al., 1987**; **Smith et al., 1989**). With these findings in mind it should come as no surprise then that re-ulceration is a common occurrence in these patients.

Two groups have measured the *forces* beneath the feet of diabetic neuropathic patients. **Stokes et al. (1975)** used a forceplate consisting of twelve beams to make measurements beneath the feet of patients with a history of plantar ulceration. For the four feet studied, a range of "highest load" was given: from 175 N to 264 N (estimated from graph). Significantly lower toe loading and more lateral forefoot loading was also observed in this group compared to a group of asymptomatic subjects.

Ctercteko et al. (1981) used a higher resolution forceplate consisting of one-hundred-and-twenty-eight, 15 mm x 15 mm loadcells for measurements. This system allowed the measurement of forces at sites of healed ulcers, which were found to be coincident with the sites of maximum load. For the twenty-four patients with a history of

plantar ulceration that were studied, the "mean peak force" was 228.7 N. Forces were also measured beneath the
feet of patients with neuropathy and no history of ulceration and beneath the feet of asymptomatic subjects. In a comparison of all three groups, a considerable overlap in the ranges of the forces measured was found. Reduced toe loading in comparison to asymptomatic subjects was also observed in this study, but in contrast to the finding of **Stokes et al. (1975)** more medial forefoot loading was observed in patients that had previously ulcerated.

When *pressures* were measured by **Proano et al. (1992)** under the toe, metatarsal, tarsal and heel areas, low values were obtained as a result of spatial averaging. Also considerable overlaps were found in the peak pressures measured under the previously ulcerated versus non-ulcerated feet of ten patients and ten asymptomatic subjects. However in an analysis of *mean* peak pressures, a significant difference was found between the pressures under the forefoot of patients that had previously ulcerated compared to the forefoot of asymptomatic subjects. Although it was not clearly stated, it appears that the sites of healed ulcers were predominantly under the forefoot, which accounts for this result.

It is interesting to note that one group of workers has made a comparison between two systems for measuring plantar pressures (**Young et al., 1992**). In the study of 20 patients with diabetes, with measurements made using the *Musgrave Footprint* and the *Optical Pedobarograph* (OPG), no significant differences were found in the maximum peak pressures measured beneath the hallux and heel, but maximum peak pressures were significantly higher beneath the first and fifth metatarsal heads when measured by the OPG. One of the reasons for these disparities was wrongly attributed to the lower measurement range of the Musgrave system, but it was correctly noted that the lower pressures measured by the Musgrave system were due to the larger sensors which led to greater spatial averaging

A number of researchers have measured peak plantar pressures in diabetic neuropathic patients and in asymptomatic subjects and have sought to define a threshold of 'normality' (**Boulton et al., 1983**; **Smith et al., 1989**) with the aim to determine which patients may be at immediate risk of plantar ulceration.

Table 1.2 Peak plantar pressures measured during barefoot walking.

Source	Peak pressures (kPa)
Boulton et al. (1983)	> 1100
Boulton et al. (1984)	920 to 3730
Smith et al. (1989)	1060 ± 590
Pollard (1984)	200 to 500
Cavanagh et al. (1987)	312 to 1895

Conclusion

With the wide range of reported pressures measured during barefoot walking under the sites of healed diabetic neuropathic ulcers (table 1.2), which in some cases overlap with the ranges reported for patients with diabetes and no foot problems and asymptomatic subjects, it is clearly difficult to define a foot pressure threshold for ulceration .

In-shoe plantar pressure measurements

Although diabetic neuropathic patients commonly ulcerate while wearing conventional shoes, there have been only few studies documenting the dynamic stresses beneath the feet of these patients inside such shoewear.

In a study of six patients (seven feet) **Pollard (1984)** found maximum peak pressures at sites of healed ulcers ranging from 220 kPa to 500 kPa (2.2 $kgcm^{-2}$ to 5 $kgcm^{-2}$) shod and from 200 kPa to 500 kPa (2 $kgcm^{-2}$ to 5 $kgcm^{-2}$) barefoot. Walking in shoes as opposed to barefoot resulted in lower peak pressures at five out of seven sites of previous plantar ulceration. In three out of five sites the highest peak pressure was found in barefoot measurements and remained so when shoes were worn. Pollard also measured pressures under areas free of ulceration, showing just a small decrease in pressures when wearing leather shoes versus barefoot walking (Table 1.3).

Table 1.3 Peak plantar pressures in diabetic patients with a history of plantar ulceration measured barefoot, shod and using walking casts by Pollard (1984, adapted)

Site	Peak pressure (kPa)		
	barefoot	**leather shoes**	**walking cast**
hallux	36	71	-
mth1	336	327	129
mth2/3	253	226	46
mth4	201	187	64
mth5	156	113	50
heel	155	137	92

Smith et al. (1989) was rather less thorough in his analysis of data in a study of eleven patients: a group average of the maximum peak pressure was quoted for seven plantar sites. This value was 610 ± 180 kPa (6.1 ± 1.8 $kgcm^{-2}$) for measurements made in-shoe and 670 ± 220 kPa (6.7 ± 2.2 $kgcm^{-2}$) for barefoot measurements. From the standard deviation of the means it is apparent that there was a considerable overlap between the in-shoe and barefoot measurements.

Conclusion

These two groups have found in-shoe plantar pressures to be only slightly reduced when patients wore conventional leather shoes compared to walking barefoot. Foot pressures therefore remain high and it appears that shoewear among other factors, may influence the magnitude of plantar pressures.

Factors associated with increased plantar pressures

Loss of protective sensation predispose patients to ulcerate at sites where pressure is still 'normal' **(Cavanagh et al., 1993)**, in addition to the link between diabetic neuropathy and high plantar pressures **(Boulton et al., 1983)**. Thus, the foot that is already at risk of injury due to loss of protective sensation is placed at an even greater risk because of high mechanical stress due to biomechanical factors, many of which result directly from **diabetic peripheral neuropathy**.

As plantar pressures in both walking and standing in normal feet are easily sufficient to occlude capillary blood flow (100mmHg is equivalent to 13.3kPa and typical pressures in the metatarsal area are around 400kPa **(Rosenbaum et al., 1994)**, it may be that diabetics are different from controls in their ability to recover from occlusion, reflected by abnormalities in a number of local reflexes, including hyperaemic response which has been shown by Tooke et al.. **(1996)** in neuropathic feet. **Diabetic microangiopathy** is an important factor to be considered in the pathogenesis of foot ulceration as discussed in Chapter 7.

1.2.10 Limited joint mobility

Connective tissue contains a great percentage of collagen. The glycosylation of collagen which can occur in diabetes, results in less flexibility with subsequent limitation of joint mobility (LJM) and less resistance to the action of collagenases **(Hamlin et al., 1975)**. Limited joint mobility was found to be related to both age and duration of diabetes **(Lawson et al., 1983)** and therefore to the duration of the non-enzymatic glycosylation process.

Several studies have also shown a three to four fold increase in prevalence of microvascular complications in patients with LJM compared to those without **(Rosenbloom et al., 1981)**. However a recent study has found that although LJM of the hands is associated with the presence of microvascular complications, does not predict their development **(Arkkila et al., 1996)**.

The normal foot has been described as a 'mobile adapter', and when this mobility is impaired **(Birke et al., 1995)** elevated plantar pressure during gait appears to result.

An association between abnormally high plantar pressures and limited mobility at the metatarsophalangeal and subtalar joints of the insensitive diabetic foot has been found by a number of researchers **(Delbridge et al., 1987, Cavanagh et al., 1991a, Fernando et al. (1991)**. Glycosylation may also change the mechanical properties of the skin and other subcutaneous tissues, making them stiffer **(Delbridge et al., 1985)** and, therefore, more likely to transmit shear to the deeper tissues. However in these patients, neuropathy is thought to be the critical factor in causing ulceration. This is backed by observing subjects who have limited joint mobility at the first metatarsophalangeal joint, i.e. having *hallux rigidus*, who have a tendency to develop an area of callus under the first metatarsophalangeal joint, but do not go on to ulcerate if they do not have neuropathy.

1.2.11 Callus formation and its effect on soft tissue properties

Callus formation is a frequent occurrence in diabetic patients; a study of prevalence of foot pathology and lower extremity complications has found that 51% patients of a diabetic outpatients clinic had plantar callus **(Holewski et al., 1989)**.

Furthermore clinical studies have reported ulcer formation to be invariably associated with plantar callus in diabetic patients with neuropathy **(Edmonds et al., 1986; Murray et al., 1996)** and moreover, haemorrhages have been found within plantar callus in a study of 100 diabetic patients **(Rosen et al., 1985)**.

In addition a significant relationship was found between certain types of foot deformity known to be associated to callus formation, and the location of ulcer in neuropathic diabetic patients **(Mueller et al., 1990)**: 6 out of 7 patients with Charcot joint had an ulceration at the midfoot, 9 of the 18 patients with compensated forefoot varus showed ulceration under the medial metatarsal heads, 15 out of17 patients with forefoot valgus showed ulceration at the first or fifth metatarsal head.

However when the relationship between the loss of protective pressure sensation and the formation of plantar callus was assessed in patients with and without insensitive feet, equivalent number of areas and thickness of callus were found in both groups of diabetic patients suggesting that additional factors such as age-related changes in the foot and footwear should be considered in the risk assessment of the diabetic foot **(Collier et al., 1993)**.

Also limited joint mobility seems to be associated with callus formation. In patients with similar limited joint mobility, but no diabetes such as those with a

rheumatoid foot, it was shown that loss of motion at the hallux due to arthritis could lead to a hyperextension deformity and painful callus formation as a result of muscle spasm of the great toe intrinsic muscles in an effort to relieve and shift pressure from the metatarsal heads **(Clayton et al., 1991)**.

Callus formation is dependent on the amount of vertical and shear forces applied on the soft tissue of the foot during gait. Even moderate pressure applied repeatedly would lead to hypertrophic callus formation, which associated with an increase in foot pressures, can lead to tissue breakdown and ulcer formation. Brand et al.. **(1988)** have described an experiment in which the same moderate stress (20PSI) was applied repetitively to the paw of the rat. In the first day a flare response, oedema and an increase in skin temperature have occurred and these changes subsided when the stress was stopped. However in the second day of constantly applied stress, the changes did not subside so readily, and histological inflammatory changes plus hyperplasia of the skin occurred. By the end of a week of repeated stress on the paw, footpad necrosis and tissue breakdown occurred. In those rats in which the application of pressure was stopped for 2 days per week, the footpad skin became hypertrophic with a thick layer of keratin **(Brand et al., 1988)**.

During activity the foot is simultaneously subjected to pressure and shear. The simultaneous application of these stresses is thought particularly destructive to soft tissue in that the magnitudes required to produce damage are reduced when they are applied concurrently **(Bennett et al., 1979)**. A theoretical analysis of soft tissue, which was initially compressed and then subjected to surface shear, has shown the effects of these stresses to be additive **(Zhang and Roberts, 1993)**

The soft tissue needs to be able to adjust and to adapt to the sudden changes in pressure in order to absorb the shock and to dissipate the peak pressures applied to the body organs and the musculoskeletal system during gait. Similar to the suspension system of a motor car, the soft tissue acts as a spring which needs to lengthen and soften to decelerate the body. Therefore the thickness and softness of the soft tissue are important in shock absorption. Subsequently skin hypertrophy leading to callus formation might occur to provide the necessary thickness. An illustration of this hypothesis is the occurrence of callus at the edge of the toes and heel, where the large changes in pressure and concomitant shear forces on the sole of the foot concentrate during gait. However if the soft tissue is not evenly distributed overall the area of the foot, the contrary is achieved, with concentration of force on small contact areas and

therefore increase in pressure **(Thompson, 1988)**. This added to the effect of callus acting as a foreign body **(Young et al., 1992)** would lead to a further increase in plantar pressure followed by tissue breakdown and ulcer formation.

1.2.12 Foot deformity

The bones, fasciae and ligaments of the foot are very important in walking forming the longitudinal and transversal arches of the foot through which the load is distributed and transmitted to the ground. They change their shape and are flexible when under load. Atrophy of the interosseous muscles associated with peripheral neuropathy leads to abnormalities in their function to modulate the action of the long flexor and extensor muscles with added effect on the metatarsophalangeal and interphalangeal joints leading to foot deformity, such as claw or hammer toes. Since the submetatarsal fat pads are attached to the flexor tendons, the fat pad could move forward as the toes become clawed. Subsequently the metatarsals could be left with only a thin covering of skin, as noted frequently from clinical observation **(Cavanagh et al., 1994)**. This phenomenon may be implicated in elevation of plantar pressures and can be a reason why plantar ulcers tend to occur predominantly under metatarsal heads.

Foot and nails deformities may also accelerate damage to the foot from repeated mechanical trauma. It has been noted that patients with diabetes who have a forefoot varus deformity, i.e. a fifth metatarsal head which is more plantar than the first, often ulcerate beneath the fifth metatarsal head **(Mueller et al., 1990; Schoenhaus et al., 1991)**. Pes cavus, an abnormally high medial longitudinal arch can also be associated with claw toes and the abnormal distribution of weight leads to excessive callus formation under the metatarsal heads. Similarly hallux rigidus leads to stiffness of the first metatarsophalangeal joint with loss of dorsiflexion and results in excessive forces on the plantar surface. Recent reports by Cavanagh et al.. **(1994)** point to abnormalities in the bone structure and ligament function of the diabetic neuropathic foot with a history of ulceration, with possible subsequent abnormalities in the forces developed under the foot and in the foot function.

Deformities due to previous surgery, such as ray amputations are normally very successful, but disturb the biomechanics of the foot, leading to high pressure under the metatarsal heads of the adjacent rays. Deformities of the hip and fractures of the tibia or

fibula can lead to shortening of the leg and an abnormal gait, which predisposes to abnormal pressure distribution and foot ulceration.

Furthermore the bony and joint destruction commonly known as Charcot foot is characteristically associated with peripheral neuropathy. Bony damage in the metatarsal-tarsal region leads to two classical deformities: the rocker bottom deformity, and the medial convexity, which can concentrate the entire weight of the body on a few square centimetres of tissue. This leads to abnormal pressures under the foot, which if are not accommodated in properly fitting footwear, would result in ulceration at vulnerable pressure points.

Conclusion

High foot pressures are frequently a consequence of deformity which would alter the mechanics of the foot leading to abnormalities in the biomechanics of gait. These external precipitating factors acting on a neuropathic foot with loss of proprioception and abnormal neuro-vascular reflexes can lead to skin injury and ulcer formation **(Apelqvist et al., 1990)**. As regards the degree of risk, the type of deformity can be classified as:

- moderate: limited ankle and hallux motion, claw or hammer toes, hallux valgus, dystrophic nails, prominent metatarsal heads or other plantar bony proeminences and calluses associated with the level of activity.
- severe: Charcot foot, greater toe or multiple ray amputations.

A definite relationship has been shown between foot deformity and location of ulcers in 40 patients with diabetes and insensitive feet **(Mueller et al., 1990)**.

These findings support the hypotheses that

- insensitivity, coupled with high, repetitive pressure, is a primary cause of ulceration
- deformity is associated with characteristic pressure patterns and callus formation.

Neuropathic oedema as mechanical factor

Oedema leads not only to microvascular consequences, but it is likely to act as a foot deformity by increasing the pressures from poorly fitting shoewear, which should also be considered as an important mechanical factor.

1.2.13 Unsuitable shoewear

Recently new methods such as F-Scan and Novel EMED-SF for dynamic plantar pressure measurements have been developed to assess the pressures inside the shoe. As they became validated and standardised, their value in quantifying the degree of foot pressure elevation in unsuitable shoes becomes clearer. High plantar pressures have been already associated with an increased risk of plantar ulceration **(Veves et al., 1992).**

The dorsal ulcers seem to occur at the interface between the upper of the shoe and foot due to possible shear stresses developed inside tight or ill-fitting shoes. Therefore in-shoe pressure measurements can be useful aides in designing and assessing the efficacy of prescription footwear in reducing raised foot pressures **(Cavanagh and Ulbrecht, 1994)** and therefore in prevention of ulceration.

1.2.14 Pattern of gait

The pressure which is loaded on different parts of the foot varies with the patient's pattern of gait. In patients with unilateral amputation, the altered pattern of gait would lead to a predominant pressure distribution on the remaining limb, therefore increasing its risk of ulceration. Indeed high pressures were found under the remaining foot in diabetic amputees **(Veves et al., 1992).** Three-dimensional kinematic data and analysis of the plantar pressures revealed a significantly greater mean peak plantar pressure and altered kinematics in the feet of 10 diabetic neuropathic patients after transmetatarsal amputation suggesting that careful postsurgical footwear management is essential if ulceration is to be prevented **(Garbalosa et al., 1996).**

The neuropathic patients have been shown to have a markedly increased postural instability (measured as the centre of force excursion) when standing with eyes open similar to non-neuropathic patients standing with eyes closed and head tilted back **Simoneau et al., 1994),** which is likely to increase their risk of falling and injury; especially as this significant increase in sway during standing and possibly during gait seems not to be compensated for by other sensory systems **(Cavanagh et al., 1993).**

In contrast, it has been clinically hypothesised that the neuropathic gait would be characterised by a lack of variability, which would lead to a repetitive pressure load on the same areas of the foot with subsequent injury to the foot. However research findings

have not supported this hypothesis pointing to abnormal variability of uncoordinated gait in neuropathic patients **(Cavanagh et al., 1992)**.

The neuropathic subjects have also been shown to have less ankle mobility, ankle movement, ankle power, velocity, and stride length during walking than the control group. A significant decrease in ankle strength and mobility appeared to be the primary factor contributing to the altered walking patterns of the neuropathic group **(Mueller et al., 1994)**.

Further biomechanical assessments are needed to investigate the effect of peripheral neuropathy on gait; one attempt has been made in this thesis when comparing foot pressures in neuropathic and neuro-ischaemic patients (Chapter 4).

1.2.15 Level of activity

It is not unusual that patients remain ulcer free although they have apparently similar elevated plantar pressure and similar significant deformity to patients who go on to develop ulceration. Among other factors which probably contribute to the difference (possibly including vascular status, plantar tissue mechanical properties, etc.) one that is frequently omitted, is the activity level of the patient.

How mobile and active the patient is at home or at work should be a common question to be asked in the Diabetic Foot Clinic, when assessing the cumulative risk of ulceration.

The level of activity can be an added factor to high foot pressures and deformity and correlates with the risk of ulceration:

- low activity level is when the patient's daily ambulation is minimal being bed- or chair-bound.
- moderate activity level is when the patient can move for more than 100 feet, similarly to when performing daily activities.
- high activity level is when the patient's occupation requires prolonged standing, walking or running **(Cavanagh, 1995)**.

Linking the risk factors

The multiple risk factors interplay in the formation of foot ulceration in the diabetic patients; leading to a final cumulative risk for ulceration. The various interacting risk factors can be reduced or enhanced, and they need to be carefully thought about when methods for treatment or prevention of ulceration are considered, because the risk factors present in an individual would determine the treatment option; for example, in the management of the neuropathic foot prescribing shoewear has to take into account the presence of raised plantar pressures and deformity plus the level of activity of each patient.

Linking the risk factors should also take in consideration the patient's psychological characteristics. **Vileikyte** et al.. (1996) have reported an association between the risk of foot ulceration and psychological factors, such as patient's interest for their own feet and in foot care, with effect on patient's (non-) compliance with treatment or prevention of ulceration.

1.2.16 Management of the diabetic neuropathic foot

Management of the diabetic neuropathic foot has three purposes: to prevent primary ulceration; to aid healing in patients who have ulcerated; and to prevent re-ulceration. All three of these processes may be aided by chiropody treatment and the use of special shoes that are often bespoke.

Walking cast and chiropody treatment of diabetic neuropathic ulcers

In the foot that has not ulcerated, callus is debrided regularly to reduce locally high pressures and minimise the risk of ulceration (**Young et al., 1992**). There are a number of ways in which the chiropodist can treat the diabetic foot that has ulcerated. In cases of primary ulceration due to continued weight-bearing, the initial treatment is in three stages: firstly, callus is removed from around the open site, as far back as soft pink skin; secondly, the area is cleaned with an antiseptic solution; and thirdly, a non-adhesive padded dressing is applied to protect and redistribute pressure at the site. At regular follow-up

appointments for chiropody, necrotic tissue is removed from around the wound to allow epithelisation from the edges and for the site to close. After the ulcer has healed, callus is debrided from the site regularly to prevent re-ulceration (*op cit*, **Tindall, 1992**).

For some patients, ulcers may be long-standing because of continued weight-bearing at the site once the ulcer has broken through the skin. In such cases treatment with a below-knee plaster cast (or *total contact cast*) is indicated in preference to the expensive alternative of hospital admission. In cases where the chiropodist allows the patient to walk in the cast, a rubber heel is incorporated into the sole - this type of cast is referred to as a *walking cast*. Plaster casts have been found to be very effective in healing plantar ulcers **(Lang-Stevenson et al., 1985; Laing et al., 1991)** possibly because of the following reasons: (1) the weight of the cast immobilises the patient and the foot is not continually weight-bearing; (2) the infiltration of tissue with fluid (oedema) is controlled and reduced by the support provided by the plaster; (3) the patient is protected from further trauma by the hard plaster shell; and (4) plantar stresses are reduced by the total contact fit.

The hypothesis that plantar stresses are reduced inside plaster casts has been investigated by three groups of workers in two studies of asymptomatic subjects and one study of patients with diabetes. Tests on asymptomatic subjects by **Birke et al. (1985)** and **Novick et al. (1991)**, showed walking casts to reduce significantly the pressures beneath the forefoot in comparison to shoes. These reductions are attributable to the total contact support of the cast, which distributes pressure beneath the foot to reduce pressure peaks.

In a study of six subjects, transducers were placed under four sites and significant pressure reductions were noted beneath the first and third metatarsal heads. Pressures were also reduced beneath the fifth metatarsal head and heel, but not significantly. Unfortunately the data recorded by these workers was not presented in units of pressure, but instead as millimetre deflections on a chart recorder. As a result, a comparison with pressures from other studies is not possible.

Another study of 20 subjects showed walking casts to reduce significantly the pressures beneath the second and fourth metatarsal heads in comparison to shoes. Pressures were higher beneath the midfoot and only slightly reduced beneath the heel in the walking cast. The increase in pressure beneath the midfoot in the walking cast compared to the shoes is attributable to the total contact support of the medial longitudinal arch and the fact that weight-bearing occurs on the rubber heel beneath this area. The data

recorded in this study was presented in pounds force for each of the transduced sites. Converting this data via transducer area to pressure, the average peak pressures for the heel, midfoot and the second and fourth metatarsal heads when wearing shoes were 634 kPa, 232 kPa, 832 kPa and 543 kPa, respectively. In the walking casts, the pressures beneath these same areas were 543 kPa, 311 kPa, 379 kPa and 289 kPa, respectively.

In a study of seven patients with diabetes (eight feet), significant reductions in both pressures and longitudinal shear stresses were noted in walking casts compared to conventional leather shoes (**Pollard, 1984**) (table 1.3). Both the plantar and shear stresses were reduced in the cast possibly due to the fact that the foot was contained and its mobility was reduced.

The total contact cast has become the standard method for mechanical unloading used in the treatment of active ulcers, which has been shown in a controlled clinical trial to heal 90.5% of ulcers in 42±29 days compared to 31.6% in 65+29 days for voluntary non-weight bearing and accommodative footwear **(Mueller et al.,1989).**

Therapeutic shoewear

Often the diabetic foot care starts with the treatment of the first ulceration. Different orthotic devices such as, centre-walking casts, walking splints and cut-out sandals, are of use to facilitate the healing of plantar ulcers in neuropathic conditions **(Birke et al., 1991)**. In addition to the standard methods, a type of 'half-shoes' has been used in the treatment of neuropathic forefoot ulcers by Chantelau et al.. **(Chantelau et al., 1993)**. They showed that the 'half shoe' cases reduced their overall healing time with 48 days and reduced their hospitalisation rate from 41% to 4%.

Clinics treating patients with diabetes have different approaches to the provision of special shoes. Some prescribe shoes to patients that are judged at risk of ulcerating, while others only provide shoes once ulceration has occurred and healing has taken place.

Ideally, the shoes supplied to patients with diabetes should be made-to-measure and have: (1) low heels to reduce forefoot weight-bearing; (2) lacing to close the quarter and hold the foot back in the shoe; (3) uppers made of a breathable material, such as leather; (4) a high toe box, so that the upper does not rub against the dorsal surface of toes; and (5) adequate depth to accommodate a flat cushioning insole or an insole shaped to the contours of the sole (*moulded insert*) that distributes pressure and reduces pressure peaks

(**Tovey, 1984**). Bespoke shoes with the above characteristics are referred to as *custom-made extra-depth shoes*, while those bought *off-the-shelf* with these characteristics are referred to as *stock shoes*.

Rocker-bottom or *rocker-soled* shoes are typically supplied to patients with a history of plantar ulceration. The outsole of these shoes is designed with a steep toe clearance that produces an axis beneath the ball about which the shoe can pivot. It is hypothesised that the axis about which the shoe pivots is critical in determining the sites beneath the forefoot at which plantar shear and pressure are reduced compared to conventional shoes. In-shoe plantar pressure measurement led **Geary and Klenerman (1986)** to advocate the placement of the rocker axis proximal to the line of the metatarsal heads. However, **Pollard (1984)** found higher pressures beneath the hallux and first metatarsal head in shoes with this rocker design, although longitudinal shear stresses were lower beneath the metatarsal heads compared to conventional shoes; while **Schaff and Cavanagh (1990)** found this rocker design to increase pressures beneath the heel, midfoot and the lateral aspect of the forefoot.

Cushioning insoles (**Chantelau, 1990**) and moulded inserts have been also described in the literature and were considered therapeutic aids for diabetic foot, but only a few studies have used objective measurements to assess their pressure attenuating effects.

Two materials are commonly used in the fabrication of shoe orthoses: PPT (Professional Protective Technology)®, a closed-cell foam; and Plastazote®[2] a rigid open-cell foam. For flat cushioning insoles PPT is used; whereas for moulded inserts both PPT and Plastazote are used, typically in a sandwich construction of *low-density Plastazote/PPT/high-density Plastazote* to produce rocker inserts. The effectiveness of these and other insole materials in reducing peak pressures beneath the foot has been shown by several researchers (**Boulton et al., 1984**; **Pollard, 1984**; **Brodsky et al., 1988**; **Smith et al., 1989**). **Spence and Shields (1968)** showed Neoprene®, a closed-cell foam (the material used to make wet-suits), to be effective in preventing blisters, calluses and ulcers beneath the feet of patients with neuropathy. Unfortunately the shock attenuation of PPT and Plastazote deteriorates in use, the Plastazote more-so than the PPT (**Pratt, 1988**). This deterioration in shock attenuation of the Plastazote is the result of "bottoming-out" compression with a consequent increase in stiffness, under repetitive

[2] BXL Plastics Ltd, 675 Mitcham Road, Croydon, Surrey, CR9 3AL, UK.

high pressure, which can be detrimental to the insensitive foot.

In summary, the prescription of fitted shoes in the management of foot ulcers aims mainly to accommodate, not to correct deformities and to distribute evenly the plantar pressures by transfer from high-pressure areas to areas of lower pressure, to provide shock absorption, to reduce friction and shear **(Janisse, 1992)**.

The shoes ought to have a proper fit matching the characteristics of the foot with:

- a heat mouldable upper to accommodate any deformities
- a long medial counter to control the heel and the medial arch and decrease the shear forces
- easy entry to the shoe with laces or velcro
- a shock-absorbing sole such as a rocker sole with an extended steel shank
- a low heel to decrease pressures on the metatarsal heads and toes
- a multiple-layer insert for the maximum cushioning and mouldability in an extra-depth.

Assessment of preventative shoewear as regards efficacy in reducing high plantar pressures and accommodating deformity and as regards the life-time of the footwear ideally requires the use of in-shoe pressure measurement techniques such as F-Scan.

Padded hosiery

As fitted shoewear is usually worn with some type of hosiery, recent studies have considered the use of padded hosiery as another management approach for reducing plantar pressures in diabetic patients **(Murray et al., 1993)** or in rheumatoid arthritis patients **(Veves et al., 1991)**. Veves and co-workers have shown that padded hosiery was able to significantly reduce the foot pressures in 27 neuropathic patients wearing only the padded socks and walking on the platform of an optical pedobarograph **(Veves et al., 1989)**.

When the effect of padded hosiery was followed-up at 3 and 6 months intervals the reduction in pressures was initially 31%, then 15.5% and 17.6% respectively **(Veves et al., 1990)**. However when the effect of padded hosiery on plantar pressures was assessed inside the shoe **(Flot et al., 1995)** it was found to be limited at the forefoot and

hallux areas of the foot, but preserved after 4 hours of continuous activity or over a period of 8 weeks of wear.

Patient education

Education is of extreme importance (**Edmonds et al., 1996**) and includes attempts to improve the patient's understanding of foot problems and how to prevent them; for example, by improving patient's compliance with prescription footwear.

However despite the accepted advantages of fitted shoewear, some patients still do not wear them (**Chantelau and Haage, 1994**):

- because the shoes are expensive and the patients might not be able to afford them, if they are not provided free of charge by NHS but only a limited provision per year.
- because the patients are unaware of the importance of the shoes in preventing foot damage.
- because the shoes are unattractive and sometimes socially unacceptable.

These points highlight :

- the necessity to provide fitted shoes for all the patients, not only for those who can afford them, at reasonable prices;
- the importance of the shoe design in their acceptability. Part of the surgical shoes effect is influenced by the length of time they are worn on or if they are worn at all or not.
- the importance of education regarding the risk of foot ulcer and how this can be reduced by wearing the surgical shoes. Here comes the advantage offered by a dynamic in-shoe system for foot pressure measurement such as the F-Scan, which permits the visualisation of foot pressures on the screen allowing the patients to see for themselves the efficiency of fitted shoes in reducing the previously high foot pressures.

An optimisation of both the design of the moulded insole and the materials used in the fabrication of the insole will lead to better preventative footwear.

Conclusion

The development of ulceration needs to be anticipated and prevented. For successful preventative foot care, patients and physicians need to understand how and why ulcers form and the rationale for the types of footwear and care necessary to prevent ulcers **(Miller, 1993)**. Proper care of diabetic foot problems should always include preventative measures such as regular callus removal, assessment and prescription of proper footwear and continuous education.

In patients at high risk of ulceration, preventative measures are a necessity not an option. Therefore a variety of bespoke footwear is usually prescribed for accommodation of deformity and relief of high plantar pressures according to their history of ulceration, to the presence of deformity and their level of activity.

For the footwear to be efficient it is important that patients are educated to understand that this is a permanent and continuous measure which requires their commitment in using and maintaining the footwear carefully.

1.2.17 Mechanisms for the development of ulceration in the diabetic neuropathic foot

The forces developed under the foot are increased because of the effect of peripheral neuropathy on the intrinsic muscles leading to the clawing of the toes , which are unable to carry the normal load leading to a transfer into weight-bearing areas towards the metatarsal heads. This is added to the effect of the atrophy of small muscles of the foot which would result in increased prominence of the metatarsal heads. These abnormal pressures underneath the plantar surface of the diabetic neuropathic foot seem to play an important role in ulcer formation.

In experimental studies, Brand **(Brand 1978)** has demonstrated that even moderate stress applied repeatedly to the foot causes inflammation, which takes more than 24 hours to resolve, so that there is a reduced tolerance the next day to similar stresses. Daily exposure to these forces would produce continuos inflammation and eventually necrosis and ulceration of the affected area.

A similar scenario would happen in the insensate feet of diabetic patients, who develop areas of increased loading due to neuropathy, deformity and callus formation. The inflammation in a normal subject is associated with pain and would lead to the subject relieving the stress by reducing the level of activity or developing an antalgic gait to reduce the load on the tender area. This does not happen in a neuropathic foot, which can not feel pain and continues to walk, while the inflammation may continue into necrosis and ulceration.

Delbridge et al.. **(Delbridge et al., 1985)** has described how in response to these stresses a plaque of keratin develops, with callus formation at the areas of high pressure, which is considered to be a pivotal mechanical factor **(Edmonds et al., 1986)** in ulcer formation.

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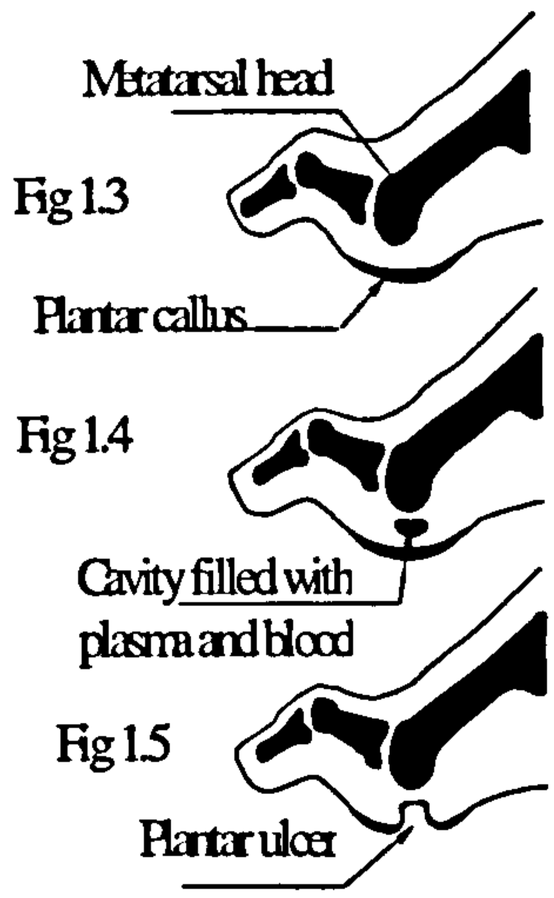
With excessive callus build-up, the compliant subcutaneous tissue between the metatarsal heads and callus becomes subjected to high local stresses during weight-bearing (**Thompson, 1988**), but the pain associated with this goes unnoticed by the patient (figure 1.3).

Breakdown of the trapped subcutaneous tissue results in a cavity filled with plasma and blood (figure 1.4). The sign of imminent breakdown is blood staining of the callus.

The cavity gradually enlarges and eventually breaks through the skin to form the ulcer (**Delbridge et al., 1985**) (figure 1.5).



When the ulcer has occurred, there is secondary bacterial contamination and infection may result. For some patients, amputation becomes necessary if bone is infected from micro-organisms present on the skin or within footwear.

1.3 The diabetic neuro-ischaemic foot

Although very little research has been conducted in the mechanisms of ulceration in the neuro-ischaemic foot, this section will describe its basic clinical features as a background to the research carried out in this thesis. As previously described, the neuro-ischaemic foot is characterised by ulceration along the margins of the foot and toes, and eventually gangrene due to a combination of peripheral neuropathy and vascular disease.

1.3.1 Diabetic peripheral vascular disease

<u>Characteristics of PVD in diabetes and its relationship to foot ulceration</u>

Abnormalities of both micro- and macro-circulation have been implicated in the aetiology of foot ulceration. Microcirculatory disorders, are known to be associated with the diabetic foot and are described in further chapters. Furthermore macrovascular disease is more common in diabetes: peripheral vascular disease (PVD) occurs 20 times more frequently in diabetic patients than in patients with no diabetes **(Ganda, 1984)**. Diabetic patients have been shown to be 22 times more likely to be admitted for skin ulcers/gangrene, 15 times more likely due to peripheral vascular disease, and 10 times more due to atherosclerosis **(Jacobs et al., 1991)**.

Macrovascular disease has the same main characteristics in diabetic as in non-diabetic patients: the atherosclerotic plaque contains lipids deposits, smooth muscle cells, monocytes, phagocytes and calcifications **(Levin, 1995)**. However there are important differences in diabetes: the atherosclerosis tends to occur at a younger age and advances quicker, sex differences are lost and men and women are equally affected **(Wilson et al. 1992)** and also the vessels below the knee are predominantly affected.

Risk factors for PVD in diabetes

The typical macrovascular risk factors such as, smoking, dyslipidemia, hypertension, obesity also predispose to PVD in diabetes. Furthermore specific risk factors such as duration of diabetes and hyperglycemia, hyperinsulinemia plus increased coagulability and thrombosis introduce an additional atherosclerotic effect.

Diabetes, predominantly Type 2, is associated with insulin-resistance and hyperinsulinemia **(DeFronzo et al., 1992)** and insulin itself has been reported to be atherogenic **(DeFronzo and Ferranini, 1991)**. The advanced-end products of glycation may play a role in accelerated atherogenesis in diabetes by interacting with the receptors of macrophages and endothelial cells with subsequent increase in matrix production and focal thrombosis **(Brownlee, 1992)** and/or with cytokines release promoting endothelial injury and plaque formation **(Vlassara, 1990)**.

The tendency for increased coagulability in diabetes is demonstrated by a threefold increase in tissue plasminogen activator inhibitor type 1 in obese and diabetic subjects compared to lean controls **(McGill et al., 1994)**.

Although both diabetic and non-diabetic patients with peripheral ischaemia can display similar clinical signs, such as intermittent claudication, rest pain and eventually foot ulceration or gangrene, different vessels tend to be affected in diabetic patients than in non-diabetic controls, who tend to have atherosclerotic involvement predominantly of the proximal vessels: aorta, iliac, femoral arteries. The most severely affected vessels in diabetes, are those below the knee, namely the tibial and peroneal arteries **(LoGerfo et al., 1984)**. This feature is typical of diabetes mellitus **(Strandness et al., 1993)**.

These vessels are often calcified in the medial wall (medial calcification), which is also a feature of macrovascular disease in diabetic patients. However the relationship between medial calcification and atherosclerotic occlusive disease has not been yet fully investigated.

1.3.2 Medial arterial calcification

This was described **(Edmonds et al. , 1982)** as a 'pipe-stem' appearance on the X-ray films in diabetic patients with peripheral or autonomic neuropathy. The medial arterial calcification was found to be significantly more pronounced in the feet of neuropathic diabetic patients than the feet of non-diabetic or non-neuropathic control subjects **(Young et al., 1993)**.

The vibration perception threshold, duration of diabetes and serum creatinine were found to be independent predictors of the degree of medial calcification. The level of serum creatinine also can be related to the association of medial arterial calcification with diabetic nephropathy **(Edmonds et al., 1986)**. As the medial arterial calcification seems to be associated with an increased risk prevalence of cardio-vascular mortality, this might be partly due to the association with diabetic nephropathy, which itself is an independent marker of increased mortality in diabetes **(Jensen et al., 1993)**.

However despite extensive vascular calcification, high peripheral blood flow at rest can be observed in the feet of patients with neuropathy **(Gilbey et al., 1989)** probably due to arterio-venous shunting, associated with autonomic neuropathy in the foot **(Edmonds et al., 1982)**

Nevertheless medial calcification seems to have an impact on the distribution of peripheral vascular disease as shown by a study of 42 diabetic patients with PVD, which demonstrated that forefoot medial arterial calcification predisposed to more severe below-knee PVD in diabetes **(Chantelau et al., 1996)** Furthermore, the medial arterial calcification can induce false readings of elevated ankle pressure in diabetic patients **(Cutajar et al., 1973)**

Methods for diagnosis and assessment of PVD in the clinic

Palpation of pulses

The main question in differential diagnosis of the diabetic foot ulcer is to recognise the neuropathic from the neuro-ischaemic foot, the important difference being the presence or absence of pulses detected by a simple and often undervalued manoeuvre, the palpation of foot pulses. If pulses of either posterior tibial or dorsalis pedis arteries are palpable, then significant ischaemia is unlikely. Absence of both pulses in the foot indicates a reduction in circulation, which ought to be confirmed by measuring the pressure index.

Doppler assessment and measurement of the pressure index

The ankle/brachial pressure index (A/B PI), which is the ratio of blood pressure measured at an ankle artery to that measured at the brachial artery is considered to be a useful tool in the assessment of lower limb ischaemia, by measuring the systolic blood pressure in the dorsalis pedis and posterior tibial arteries, and if carefully performed it reflects closely the intra-arterial pressure (**Bollinger et al., 1976**). The pressure index is <1 in the presence of ischaemia, whereas in normal subjects is usually >l. Thus, absence of pulses and a pressure index of < 1 confirms ischaemia. Conversely, the presence of pulses and a pressure index of 1 should rule out ischaemia. This would determine the ulcer management, namely that peripheral vascular disease is not present and the ulcer is treated as a purely neuropathic one, without considering angiography or angioplasty.

However some diabetic patients have non-compressible peripheral vessels giving an artificially elevated A/B PI, even in the presence of ischaemia. Falsely elevated A/B PI measurements may be associated with medial calcification (**Edmonds et al., 1986**); thus they could lead to a subsequent high value despite the presence of peripheral vascular disease. In a study of 2092 patients referred for PVD assessment, Goss et al.. (**Goss et al., 1989**) have shown increased prevalence (18.3%) of a raised A/B PI(>1.5) in IDDM patients more than in NIDDM patients (4.5%) , and in non-diabetic controls (2.8%). The

increase in prevalence of a raised A/B PI with duration of diabetes was found to be in agreement with the increase in prevalence of medial calcification with the duration of diabetes (**Ferrier, 1964**). These findings of elevated A/B PI might interfere with treatment decisions in diabetic neuropathic patients with concomitant peripheral ischaemia.

It is thus difficult to assess the diabetic foot when the pulses are not palpable, but the pressure index is > 1. There could be two explanations. The examiner may have 'missed' the pulses particularly in an oedematous foot and should go back to palpate the foot after the vessels have been located by Doppler ultrasound. If the pulses remain impalpable, then ischaemia probably exists in the presence of medial wall calcification **(Edmonds et al., 1982)**.

Considering these limitations of the ankle/brachial index other modalities for assessment of peripheral vascular disease have been proposed, such as a computer-based test using the A/B PI and a treadmill exercise for diagnosis of intermittent claudication **(Goss DE et al., 1988)**.

Toe systolic pressure

In order to avoid errors of diagnosis of critical limb ischaemia additional methods are recommended, such as hydrostatic toe systolic pressure (**Chantelau et al., 1995**). Measurement of toe systolic pressure requires a toe cuff and a device for detecting toe blood flow. A toe pressure of 30 mmHg or less indicates critical ischaemia and suggests a very poor prognosis (European Working Group on Critical Leg Ischaemia, 1992).

Transcutaneous oxygen tension

This has been also been proposed as a useful method with which to assess the functional status of skin blood flow. A recent study has demonstrated the value of measuring transcutaneous oxygen pressure on the skin of the dorsum of the foot in patients suspected of having critical ischaemia. The reduced values observed in diabetic patients have been interpreted as a consequence of peripheral vascular disease (**Uccioli**

et al., 1994). All patients with low oxygen pressure of less than 30 mmHg had clinical evidence of critical ischaemia **(Jacobs et al., 1992).**

Angiography

If critical limb ischaemia is diagnosed and serious lesions such as rest pain with or without gangrene develop, putting the limb at risk of amputation, angiography is performed with the possibility for angioplasty or by-pass if significant artery stenosis is detected **(Edmonds et al., 1986).**

Other vascular tests

Recently a new method investigating the capillary circulation of the foot with 99mTc-macroagregated albumin perfusion scanning was also proposed as an effective predictor for healing; it correlates findings of a poor tissue perfusion with failure of the ischaemic ulcer to heal **(Moriartry et al., 1994).** However this method has not been employed in general use.

Laser Doppler measurements have also been used in assessing the micro- and macrovascular changes in patients at risk of foot ulceration, and their association with other non-invasive methods could be used in assessment of neuro-vascular reactivity in diabetic subjects with neuropathy.

<u>Conclusion</u>

A variety of vascular tests can be employed in the diagnosis of peripheral vascular disease in diabetes, of which the most commonly used for screening of neuro-ischaemic patients in the Diabetic foot Clinic at King's College Hospital are palpation of pulses and ankle-brachial pressure index. In the case of those with suspected calcified arteries, transcutaneous oxygen tension is also measured.

1.3.3 Neuro-ischaemic ulcer

The initial presentation of the neuro-ischaemic ulceration is commonly as a area of superficial tissue necrosis which can be painful, surrounded by a rim of erythema, unlike the pure neuropathic ulcer which is not painful and presents frequently as a plantar lesion surrounded by callus.

The neuro-ischaemic lesions occur mainly on the margins of the foot, such as the great toe or the lateral borders of the feet. The ulcers tend to be shallow, and not associated with callus. Foot pulses are usually absent.

Claudication in a diabetic with PVD requires close and regular follow-up although claudication alone would rarely require surgical intervention. However rest pain when it develops in a pink, ischaemic foot is always serious. Digital gangrene may follow, and spread, and is much more serious than in a purely neuropathic foot. These changes in the neuro-ischaemic foot often lead to major amputation, if angiography, followed by angioplasty or by-pass are not performed immediately.

1.3.4 Management of the neuro-ischaemic ulcer

Medical management

This is recommended for some of the patients with ischaemia who tend to be elderly, frail and/ or with other diabetes complication such as diabetic nephropathy or widespread cardiovascular or cerebrovascular disease, for whom reconstructive surgery is not feasible. Ischaemic ulcers may be painful and it may be necessary to prescribe opiates.

Eradication of infection with prompt and specific antibiotic therapy in consultation with the microbiologist is recommended as in the purely neuropathic foot. However, severe sepsis in the ischaemic foot is an indication for emergency admission, first to control sepsis by intravenous antibiotics and surgical drainage, and secondly to assess the possibility of revascularization either by angioplasty or reconstruction.

Chiropodial treatment

This is not aimed for removal of callus, as neuro-ischaemic feet tend not to form callus in excess, but toward removal of necrotic tissue from the ulcers and, in the case of subungual ulcers, cutting back the nail to allow drainage of the ulcer (**Foster et al., 1989**).

However if any lesion, however small and apparently trivial has not responded to conservative treatment within 4 weeks, then angiography and revascularization should be considered; and when critical ischaemia is present, this referral ought to be initiated much earlier (**European Working Group on Critical Leg Ischaemia, 1992**).

The neuro-ischaemic foot with gangrene is treated differently than the neuropathic foot. When it is possible to improve the circulation by arterial reconstruction, then digital amputation can be performed in the ischaemic foot. When revascularization is not feasible, the amputation of a necrotic toe should not be performed because its healing is unlikely. However, regular debridement by the chiropodist along the demarcation line (**Foster et al., 1989**) could lead to successful autoamputation, as long as infection is controlled, in which the necrotic digit drops off to reveal a healed stump.

Extensive gangrene in the neuro-ischaemic foot is either due to severe sepsis or complete occlusion of both the superficial femoral and deep femoral arterial systems. Sepsis should be controlled by surgical drainage and intravenous antibiotics. Then urgent angiography would be required to assess the possibility of arterial reconstruction.

Surgical revascularization

Techniques of revascularization of the diabetic foot years have been developed in recent years. Angioplasty in the iliac, superficial femoral and popliteal arteries is often performed in patients with localised disease, for example stenosis or short (< 10 cm) occlusions. However, diabetic patients tend to have lesions in the arteries below the knee, but advances in catheter and imaging techniques have made it possible to perform

angioplasty in these arteries, although the long-term results are still under appraisal **(Bakal et al., 1990)**.

Arterial bypass in the leg, and distal bypass either to the tibial or peroneal vessels is vital in cases of severe sepsis and necrosis to re-establish blood flow to the diabetic foot **(Edmonds, 1987)** and diabetes is not considered anymore a contraindication.

Prescription footwear

Footwear is frequently needed in the neuro-ischaemic foot. Unless there is severe deformity, when bespoke shoes are recommended, an extra-depth ready-made shoe to protect the margins and accommodate the foot should offer adequate protection and prevention of ulceration.

1.3.5 Mechanisms for the development of ulceration in the diabetic neuro-ischaemic foot

The pressure between some parts of the foot and the surface of the foot, on standing, could be sufficient to stop the blood supply to those areas. If the neuro-ischaemic foot, ischaemic necrosis may occur in the case of tight new shoes maintaining a pressure on the skin of the foot when worn for the first time.

The forces required are not high (7-14kPa) but can lead to ulceration **(Brand, 1978)** if maintained for several hours or by continuous friction with the shoe interface, especially if it is too tight. If the arterial blood flow is also reduced due to underlying peripheral vascular disease, then the skin perfusion could be stopped by an even smaller pressure. Thus arteriosclerosis is considered to be a predisposing factor for ulceration, especially in neuropathic patients with decreased sensation in their feet, who would not be able to identify the discomfort arising in shoes which are too tight.

The response to such pressure is different in the neuropathic foot compared with the neuro-ischaemic foot. In the neuropathic foot, the response to pressure is hyperkeratosis and callus formation with eventual ulceration **(Edmonds et al.. 1986)** whereas in the neuro-ischaemic foot, pressure may lead to direct tissue damage.

1.4 Conclusion of introduction

This introductory chapter has described the multiple risk factors involved in the aetiology of the diabetic foot of both neuropathic and neuro-ischaemic origin.

One of the most important risk factors, present in both types of diabetic foot, is diabetic peripheral neuropathy. This along with other predisposing factors due to the presence of diabetes, such as diabetes duration and long-term complications, diabetes control and soft tissue abnormalities plus epidemiological risk factors: history of foot ulceration, social status and race, put the diabetic foot at considerable risk of ulceration.

In the neuropathic foot, elevated plantar pressures are the other main factor which can precipitate ulceration. Extrinsic mechanical factors, such as stepping on a pin and biomechanical factors, such as foot deformity, limited joint mobility, abnormal pattern of gait and level of activity, plus the formation of callus and unsuitable footwear, are all factors associated with increased plantar pressures in the diabetic neuropathic foot.

Thus the need to measure plantar pressures inside the shoe of the patient at risk and in normal walking conditions, requires the use of a methodology which would not interfere with any of the above mentioned mechanical factors.

Furthermore a reproducible and sensitive technique of foot pressure measurement is needed for the quantitative assessment of therapeutic interventions used to reduce plantar pressures, such as removal of callus and provision of footwear.

The neuro-ischaemic foot , which is characterised by the presence of diabetic peripheral vascular disease and neuropathy, has also a high risk of ulceration. From observational studies it is known that diabetic neuro-ischaemic patients tend to ulcerate on the margins of the foot and form less plantar callus. Nevertheless the other main factor involved in ulceration, the foot pressures and their pattern of distribution have not been studied in the neuro-ischaemic foot.

Diabetic microvascular disease has been associated with the foot at risk of ulceration. Abnormalities in skin axon reflexes have been demonstrated in the neuropathic foot. However the effect of neuropathy on the function of microvascular

wall components, i.e. the endothelium and smooth muscle function, has not been previously investigated.

Table 1.4 Comparative characteristics of the neuropathic and neuro-ischaemic foot

	Neuropathic Foot	*Neuro-Ischaemic Foot*
Peripheral neuropathy	present	present
Macrovascular disease	absent	present
Microcirculatory abnormalities	present	present
Callus	present	absent
Site of ulceration	plantar	margins of foot
Foot pressures	elevated	unknown
Pattern of pressure distribution during gait	variable	unknown

It is surprising that relatively little research has been carried out in the investigation of factors leading to ulceration in the neuro-ischaemic foot, especially with regard to its distinctive characteristics from the neuropathic foot.

Therefore research in determining the risk factors for the neuro-ischaemic as well as the neuropathic foot is needed. Exploring the intrinsic mechanisms through which all these risk factors interact and eventually lead to ulceration may provide a better understanding of the pathogenesis of foot ulceration, which then could be used in designing prevention and therapeutic strategies.

Chapter 2. AIMS OF THE THESIS

The diseased diabetic foot especially if neglected and followed by gangrene and amputation, is one of the most important complications of diabetes in terms of morbidity and healthcare costs.

Reducing its incidence by adequate prevention and treatment can only be done if the pathogenesis of ulceration in the diabetic foot is fully researched and understood. However the understanding of the multiple factors, such as foot pressures, diabetic neuropathy and vascular disease and their interactions in the pathway to neuropathic and/or neuro-ischaemic ulceration requires further research.

The aims of this thesis were four fold:

1. to establish a novel, practical and reproducible methodology for measurement of plantar pressures inside the shoe during normal walking conditions.

2. to measure the plantar pressures under the neuro-ischaemic foot in comparison to the neuropathic foot using the newly established methodology, exploring the hypothesis that foot pressures may be responsible for the difference in the sites of ulceration in the two types of diabetic foot and in order to understand better the role of foot pressures and their interactions with other factors involved in the pathogenesis of ulceration in diabetes.

3. to quantitatively investigate

- the effect of formation and then removal of callus on plantar pressures,
- the degree of plantar pressures reduction achieved with different types of footwear, exploring the hypothesis that therapeutic interventions, which are routinely used in the Diabetic Foot Clinic, are efficacious in reducing elevated foot pressures.

4. to explore the effect of neuropathy on the endothelial and smooth muscle performance with the hypothesis that microvascular function is influenced by the presence of neuropathy in the foot prone to ulceration.

Chapter 3. FOOT PRESSURES MEASUREMENT

3.1 Background

The forces acting on the plantar surface of the foot which consist of two components: vertical forces or direct pressure normal to the surface, and shear forces tangential to the surface, play an important role in the aetiology of the foot. Therefore measuring these forces would be useful in diagnosis and assessment of foot disorders associated with peripheral neuropathy, Hansen's disease, spina bifida and orthopaedic conditions. In diabetic neuropathy, a relationship between high foot pressures and foot ulceration has been reported (**Ctercteko et al., 1981; Veves et al., 1992**). The abnormally high pressures occur in an insensitive foot which lacks the ability to detect and respond to noxious stimuli and therefore fails to redistribute these pressures leading to ulcer formation. The shear force has also been shown to have a cumulative effect with vertical force and contribute to ulcer formation (**Bennett et al., 1979**). Measuring the forces in the foot would allow preventative measures to be undertaken to reduce the risk of foot ulceration.

The 'ideal' system for foot pressure measurement as defined by Cavanagh et al. (**Cavanagh et al., 1992**) underlines the Kelvin's law: the act of measurement should not interfere with the characteristics being measured. Therefore an 'ideal' device for plantar pressure measurement would cover a dynamic range of pressures from 0-2Mpa, with a linearity of <5% full scale, a sampling rate >50Hz, an amplitude resolution <10kPa, a spatial resolution <1mm^2, a hysteresis <5%, and a thermal stability <5% for 10°C change in temperature. The importance of spatial resolution in assessing peak plantar pressures has been stressed recently by Cavanagh (**Cavanagh et al., 1996**), but in clinical use it may not be necessary to assess the overall pressures but the localised areas under metatarsal heads most prone to ulceration, which describe an ellipse (approximately 1/0.5cm) and therefore it may be possible that small pad sensor or localised analysis of foot pressures would be more adequate for clinical use. Regarding the frequency of sampling, a high sampling rate is necessary if jumping or running measurements are done, but if neuropathic patients who walk slowly are to be assessed, lower frequencies are still acceptable.

However at the moment the results from different groups doing clinical research in foot pressures cannot be compared because of differences in sensor size affecting the resolution of devices and non-standardised collection of data protocols. Furthermore plantar pressure units are not standardised.

In a recent paper from the Foot Pressure Interest Group, which is working towards standardisation in foot pressure measurement **(Barnett, 1996)** the need for standard user calibration, such as a standard sampling rate, was expressed. Also a spatial resolution of up to 5mm was considered to be acceptable.

Likewise, considering the variety of methodologies used for foot pressure assessment, the need of standardisation arises once more in order to allow comparisons between studies. Some groups use long walkpaths, which allow 3 steps before and after the force plate, therefore measuring mid-gait pressures, whereas others use the' first step' pressures; however both methods are considered to be rigid and interfere with the 'normal' walking. Therefore free walking is recommended. This would also preserve the patient's normal pace, whereas when a metronome is used to control the walking speed, this can induce alterations in the normal cadence. When analysing the measurements, the peak plantar pressures and pressure time integrals would be advisable to be quantified from a mean of 3-5 steps, which are considered to be suitable for interpretation of foot pressures.

Several systems for barefoot and more recently for in-shoe measurement of plantar pressure are commercially available. They have enabled researchers to make clinical investigations which were hitherto impracticable. In-shoe sensors can make a potentially valuable contribution to the design and prescription of footwear and orthoses **(Rose et al., 1992; Corbett et al., 1993; Albert and Rinoie, 1994; Lord and Hosein, 1994)**, and in addition can enable further exploration of the causative factors of foot problems, notably those of diabetic ulceration, in realistic shod conditions **(Cavanagh et al., 1985; Pitei et al., 1995)**.

3.1.1 Systems for assessment of shear forces under the foot

Shear forces are thought to play a key role in pathogenesis of foot ulceration. The role of shear stresses in the aetiology of ulcer formation was stressed by Bennett et al. **(Bennett et al., 1979)** who showed that if shear forces act simultaneously with vertical ones, only 50% of vertical forces would be enough to occlude the blood flow in the foot. Reduced blood flow may decrease the tissue repair ability and lead to ischaemic lesions. However techniques for measurement of shear forces are not so well developed as those for the assessment of vertical forces. This is because of the technical difficulties arising from the fact that placing a transducer inside the shoe would interfere with the normal shear stresses by accentuating them. However one of the first attempts to develop a discrete shear transducer were made by Tappin and Pollard **(Tappin and Pollard, 1980)** and later by Lord and Hosein **(Lord and Hossein, 1992)**. Both transducers used the same magneto-resistive principle: the movement of a magnet relative to a magneto-resistive element is proportional to the applied force and leads to a change in resistance. The maximum excursion of 0.6mm corresponds to a shear stress of 250kPa. The shear transducer developed at King's College School of Medicine and Dentistry was based on the same magneto-resistive principle, and was able to measure not only shear in two orthogonal directions but also direct pressure. It was aimed to place the transducer under the metatarsal heads. These were detected by direct palpation or by a novel approach, using a F-Scan pressure-measuring insole to detect the areas of maximum pressure on the map of the foot. The peak pressures measured under the palpated markers were on average only 50% of the true peak recorded by F-Scan suggesting that the method of palpation mislocated the area of peak pressure **(Lord and Hosein, 1992)**. These findings highlight one of the problems occurring with discrete transducers, whether for assessment of shear or vertical forces, in placing and maintaining them in the correct position under the foot. Another clinical study **(Pollard et al., 1983)** using shear transducers in normal subjects was done barefoot and in a variety of footwear. They found the longitudinal shear under the first metatarsal to be the greatest in barefoot walking, whereas the walking cast reduced both the longitudinal and transverse components of the shear forces plus the vertical forces offering both a mechanical explanation for the healing of neuropathic ulcers in a plaster cast and an insight into a possible mechanism of ulcer formation. A study of relative timing of shear forces on the sole of the forefoot during walking **(Tappin et al., 1991)** has also

described the cumulative effect of shear and vertical forces in time: the maximum shear stress occurred at the same time as the maximum vertical stress under the first and fourth/ fifth metatarsal heads.

The shear force transducers await further development **(Laing, 1992)**. Recently a new type of shear transducer, the Kent shear system was introduced. It uses piezoelectric copolymer film for in-shoe biaxial shear force measurement: **(Akhlaghi and Pepper, 1996)**. This system using a 10x10x3.6 mm copolymer film transducers has been developed to allow the simultaneous measurement of two orthogonal shear forces , at four sites under each foot over multiple footsteps in every day footwear. and it has been shown that this system successfully measures in-shoe shear forces. Further research is needed to demonstrate the effect of shear forces on the skin and soft tissues of the foot and their role in the foot pathology.

3.1.2 Systems for assessment of vertical forces under the foot: barefoot and in-shoe measurements

Barefoot measurements

Force and load distribution measurement platforms have been used for static and dynamic measurements of foot pressures. The Kistler force plate (Kistler Instruments Ltd., Whiteoaks, The Grove, Hartley Wintney, Hants, UK) measures total vertical and shear forces with an accuracy greater than 1% and sensitivity to 0.05Pa, over full-scale ranges of 200kPa for vertical forces and +/- 50kPa shear forces. However the system is not able to measure plantar load distribution being mainly used for gait analysis. Nevertheless the high specification, good repeatability and long-term stability have recommended the Kistler force plate as the 'Gold standard' for plantar loading measurements **(Cobb and Clermont, 1995)**.

The Musgrave Footprint system (Musgrave Footprint, Preston Communications Ltd., Llangollen, Clwyd, UK) is a method for the measurement of plantar load distribution under the barefoot. Its force-sensing resistors consist of two polymer sheets: one coated with pectinate electrodes, the other with semiconducting material. When the

force is applied, the contact area between the two layers increases leading to a logarithmic change in resistance. There are 2048 3*3mm sensors in a matrix distribution. A sensor's response to a load above 110kPa can vary by 2% per loading cycle; above 1000kPa the variability increases to 15%. The temperature coefficient is load-dependent around 0.1% per Kg°C-1 and a possible clinical limitation could be the reduction in sensitivity with increasing load (**Cobb and Clermont, 1995**). In clinical studies a period of accustomisation was always necessary as demonstrated in a study on 86 healthy subjects (**Bennet and Duplock, 1993**) or in another study assessing the effect of reconstructive surgery for different foot conditions (**Roggero et al., 1993**).

The optical pedobarograph is a high-resolution technique for imaging the plantar load distribution being particularly advantageous for detection of sites of high pressure. This is extremely important, as highlighted by Lord and Reynolds (**Lord and Reynolds, 1986**), in early detection of areas at risk of foot ulceration.

The pedobarograph consists of a glass plate covered with an opaque material, typically a plastic sheet (**Betts and Duckworth, 1980**). When the force is applied, the change in the contact level between glass and plastic leads to a change in the amount of light propagated in the glass plate with a change in the refractive index, areas of contact showing as low-intensity regions (**Franks and Betts, 1983**). There is a range of transducer materials raising various problems such as adhesion to the glass plate, material deformation and wear, saturation within the range of interest, poor dynamic response time, dependence on the surface granularity, non-linearity, although the best transducer materials can reach a linear relationship between the pressure and light intensity (**Franks and Betts, 1988**). The pedobarograph is also dependent on temperature with a variation of 10-15% over 20-30°C. Numerous clinical studies have used the pedobarograph in orthopaedics (**Betts et al., 1980**)or in diabetic foot (**Boulton et al., 1987**).

Another optical technique for high resolution imaging of foot pressure was developed by Rhodes et al. (**Rhodes and Sherk, 1988**) using an photoelastic sheet and a polariser bonded to a walkway, which is comparable to the pedobarograph with the advantage of temperature-independent responses (**Cobb and Clermont, 1995**).

In-shoe pressure measurements

In-shoe foot pressure measurements have two main advantages over the barefoot measurements: they assess the forces developed at the shoe-foot interface, mostly implicated in the foot ulcer formation **(Cavanagh et al., 1992)**, and it is possible to determine these forces during different gait phases **(Hennig and Cavanagh, 1994)**.

Discrete transducers for in-shoe pressure measurements

The in-shoe discrete transducers which allow in-shoe pressure measurement at specific plantar sites introduce the risk of inadequate placement of the transducers in relation with the areas of interest **(Lord and Hosein, 1992).** However an accurate method of locating the discrete transducers was used by Akhlaghi et al. **(Akhlaghi and Pepper, 1996)** in a study highlighting the importance of using in-shoe pressure measurements of multiple steps in comparison to single-strike force plates, which give variable results.

The capacitive pressure transducers respond to application of force with a change in capacitance; their sensitivity varies over the sensor area reducing from the centre, where this is ±5kPa, to ±30kPa at periphery; therefore accuracy of the output depends on the load distribution. The frequency response is 12Hz, limiting measurement to slow walking speeds as described by Kothari et al. **(Kothari and Webster, 1988),** who proposed their use as an 'electrotactile' feedback system to restore sensation to patients with diabetic neuropathy.

The piezoelectric ceramic transducers are placed in a polyurethane case not only to protect them from moisture, but also to allow an even distribution of pressure and reduce the sensitivity to lateral strain **(Gross and Bunch, 1988)**. The piezoelectric transducers using a copolymer film such as polyvinylidene fluoride (PVDF) were located into a 3mm thick lacquered cork insole at eight sites **(Nevill et al., 1995)**. Although their technical characteristics were better than those of the ceramic ones (non-linearity 1.5% vs 3.4%, hysterisis <1.5% s 5.8%, frequency repines >20Hz vs >50Hz), the transducers using a copolymer film required periodic relaquering to reduce charge leakage arising from in-shoe humidity. These discrete transducers can still introduce errors by concentrating the load at the measurement site with consequent high readings

or saturation, ideally the thickness of the sensor should be below 0.5 mm to avoid these errors (**Ferguson-Pell, 1980**).

The Electrodynagram system (Langer Biomechanics Group Ltd., The Green, Cheadle, Stoke-on-Trent, UK) uses seven sensors with a thickness of only 0.3 mm and contains an integrated circuit with a resistive bridge. It has been used in studies of diabetic foot ulceration (**Smith and Plehwe, 1989**) or in assessing the effect of heel height on foot function (**Gastwirth and O'Brien, 1991**) because it allows both in-shoe and barefoot pressure measurements.

An electro-optical force transducer containing a spring mounted in an extra-depth shoe acts to occlude transmission of light between a LED and a photodetector (**Maalej and Webster, 1988**). However this would be difficult to use in clinical practice because it requires fitted footwear and it is difficult to align the sensors.

In conclusion, although discrete transducers are advantageous by assessing the forces at the shoe-foot interface and allowing the correlation of load distribution with the different phases of gait, their mechanical properties such as thickness and size can also significantly affect the pressure distribution.

Insole transducers for in-shoe pressure measurement

A solution to the mechanical drawbacks of the discrete transducers can be to incorporate numerous transducers distributed in a matrix system in an insole, which would be placed inside the shoe with minimal effect on gait and pressure distribution. Insoles containing an array of piezo-electric transducers were developed. Hennig et al (**Hennig and Cavanagh, 1982**) constructed an insole with 499 piezo-electric ceramic transducers contained in a silicone rubber, with good technical characteristics: 0-1500kPa measurement range, 0.5kPa sensitivity with 1.5% variation over 10-40°C, non-linearity ±2% and hysterisis 1%, but requiring individual calibration for each sensor because of variation in their individual sensitivity. This type of insole can be difficult to build and can develop rapid mechanical fatigue, which can be avoided by using piezo-electric polymer (PVDF) film (**Pedotti and Assente, 1984**). Sixteen circular metallic discs were englobed into the film and the variability between sensors was much reduced ±3%.

However for both types of piezoelectric insoles a few sources of error were discovered: additional charge generation due to lateral stretching, compressional heating and frictional heating during gait **(Cobb and Clermont, 1995)**.

The EMED Pedar system (Novel Gmbh, 80802 Munchen, Germany) has a capacitive sensor matrix. The insole consists of 99 sensors and it is 2mm thick, with individual sensors occupying an area of 17mm2. The sensor range is 30kPa-600kpa with a sensitivity of 1kPa varying by ±5% over a temperature range of 10-40°C. It has a low hysteresis <3%, frequency response to 50Hz and good (intraclass correlation coefficient=0.84) day-to-day variability **(McPoil et al, 1995)**. Due to its reliability the EMED has been used extensively in biomechanical studies and in clinical trials involving patients with diabetic foot ulcers **(Cavanagh et al., 1992)**.

Conductive and resistive technologies have been also employed in recent years in foot pressure analysis. An insole was developed by Peruchon et al. **(Peruchon et al., 1989)** to measure variation in conductance of a conductive polymer when force is applied. Each sensor consists of a ground and an outer electrode, the current between electrodes increases with compression of polymer. The technical characteristics are less impressive; from 0-225kPa material compression is 15%, hysterisis is 12%, and non-linearity is 16%, after 225kPa nonlinearity increases to 26%. The measurement range is 0-300kPa with a sensitivity of ±20kPa, but the response is temperature independent for 15-35°C. The Podo-Dyno-Gram system (PKS Electronics, Belgium) has been recently developed. It has an insole consisting of a mylar substrate which contains 64 circular sensors. They are force-sensing resistors with a measurement range of 0-800kPa and a sensitivity ±20kpa, non-linearity is less 10% **(Cobb and Clermont, 1995)**.

The F-Scan (Tekscan Inc., 307 West First Street, South Boston, MA 02127-1342, USA) is a system used fairly widely with a stated sensitivity of ±4%kPa. This is based on Force Sensitive Resistor (FSR) technology, which offers the advantage of very thin construction together with high spatial resolution. This concept was first introduced for medical application as a dental bite sensor **(Podoloff and Benjamin, 1989)**, and is now available for applications in gait analysis, prosthetic socket design, prosthetic knee joint design and seating.

Conclusion

The in-shoe foot pressure measurements give valuable information about the forces developed at the foot/shoe interface, information which, the platform systems such as the Kistler force platform and the pedobarograph, although reliable, fail to do.

The discrete transducers however are difficult to place and maintain at predetermined anatomical locations on the foot, because they can migrate due to the lateral stresses developed at the foot-shoe interface. This also means that the foot pressures cannot be assessed in the areas of the foot between the transducers. They also can act as foreign bodies in the shoe and alter the pressure measurements.

However the matrix devices for in-shoe measurements, such as the F-Scan system, which consist of a large number of sensors evenly distributed permit an overall assessment of foot pressures and allow visualisation of pressure distribution inside the shoe.

They also have the advantage in comparison with more traditional platform that the data can be collected from multiple steps without the risk of "targeting". Patients do not need to alter their walking pattern to make contact with the platform.

Their disadvantages are related to the fact that they are more susceptible to mechanical breakdown as they are placed in and out of the shoe or subjected to repeated loading on the same area. They are more exposed to the in-shoe conditions of temperature and humidity and uneven contour. The position of the sensor relative to the floor influences the type of force measured, the true vertical forces are measured on the platforms whereas the in-shoe insole at its best, would probably measure the 'normal' pressures because of its position to the ground (**McPoil et al., 1995**).

Nevertheless the in-shoe pressure measurements are essential for the clinical understanding of ulcer formation and also for the design and assessment of prescription footwear to maximise its benefit to the patient.

3.2 F-Scan - a new method of foot pressures measurement

One of the matrix systems for in-shoe foot pressure measurement is the F-Scan system which uses a pressure-sensitive insole placed inside the shoe, connected to a computer. The distribution of the vertical plantar pressures developed inside the shoe during normal walking conditions can be visualised instantly, recorded and analysed in order to detect the areas of peak pressures, the most prone to ulceration in a diabetic neuropathic foot.

3.2.1 Description of the F-Scan system

The system provides an ultrathin (0.16mm) and flexible pressure-sensitive insole to be placed inside the shoe. The insole was trimmed specifically to fit the shoe shape and size, by following the concentric tracings indicated on the insole which corresponded to different shoe sizes for men, women, girls and boys. The patients are asked to slip their foot inside the shoe very carefully because the insole can be easily creased. This is also why the handle extending from the side of the insole needs to be reinforced with sellotape at the points of insertion.

Fig. 3.2.1 The F-Scan insole is placed inside the shoe and inserted directly in an amplifier fixed to the ankle of the patient

The handle connects directly into a cuff unit attached to the patient's ankle to provide preamplification and signal conditioning. A 9.25 m long coaxial cable links the amplifier to an IBM-compatible personal computer with an interface board, which runs F-SCAN Gait Analysis software version 3.65 to store and analyse the data.

3.2.2 Recording technique

The recording parameters can be set to suit the type of study undertaken: the range of frames to record is 1-285, the frequency expressed as frames per second is 0.000250-126.9Hz, the period range is 0.007878-4000.0 seconds per frame. Once the insole is placed inside the shoe and the patient is ready to start the test, the "recording" function visible on the screen is clicked and the F-SCAN displays 'live' the map of the foot and the gait sequence on the screen.

Fig. 3.2.2 Recording technique for the F-Scan system of in-shoe foot pressure measurements

Then the recording is processed by the computer and the data can be saved on the disk. 'On the spot' or later the recording can be re-installed using a 'Playback' function, when the F-Scan operates similar to a video-recorder.

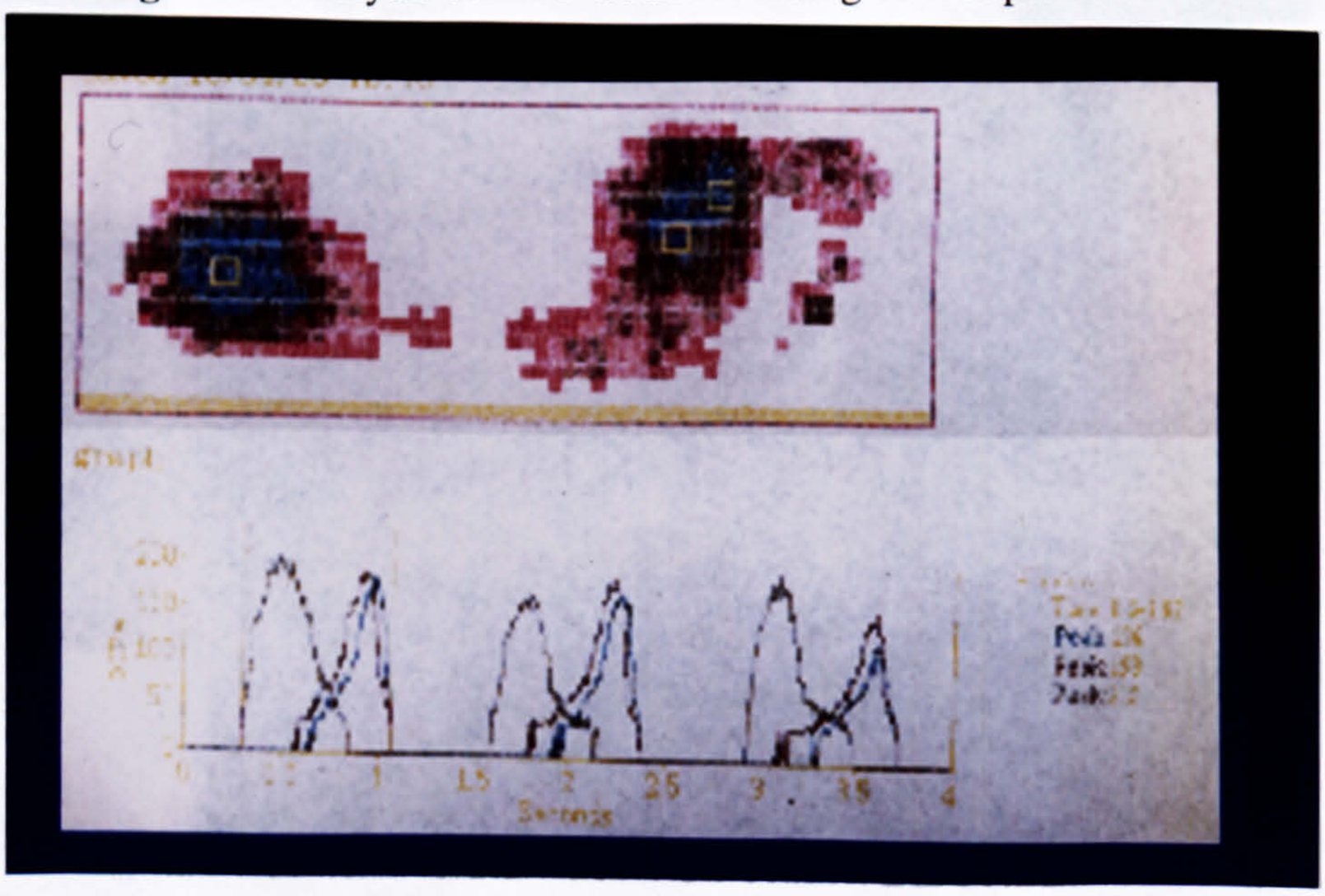
3.2.3 Calibration technique

The subjects are weighed before starting the first run. Then their weight is entered into the system, which is to be calibrated against each individual weight. The subjects are asked to stand on a single foot for 2-3 seconds looking straight ahead and, taking a little support, if needed, to reduce sway and load their entire weight evenly on one foot. When the pattern of pressure loading is seen to be stabilised and distributed evenly on the screen, the calibration system is triggered. The procedure is repeated then for the other foot.

3.2.4 Analysis of the recording

F-SCAN data recorded from different runs can be recalled and analysed in one or two active windows side-by-side on the screen. The gait mode displays a two-dimensional representation of the plantar pressures sequentially from heel-strike to toe-off. The increase in pressure is seen as a change in colour of the pressure map from blue to red as a function of time.

Fig. 3.2.3 Analysis of the F-Scan recording of foot pressures



When the "Average" function from the screen is activated a smoothing effect on the immediate surrounding cells occurs and reduces the possibility of artefacts.

In order to measure the peak pressures at different locations on the plantar surface of the foot, the analysis allows up to four areas of interest (boxes) to be assessed by the operator. The boxes are adjustable to fit the area of interest from a minimum of 10*10mm (2cells*2cells) to a maximum of 300*105 mm (60cells*21cells) covering the entire field for one step. The boxes can also be moved in different locations on the map of the foot allowing the investigator to assess plantar pressures in a specific area of the foot, such as forefoot or heel.

The F-Scan software enables analysis of the vertical ground reaction force versus time, the pressure versus time or the peak pressure versus time. The actual values can be obtained from the graphs for the areas of interest in each recorded step.

The centre of force path, which is the path that the maximum pressure follows from the heel to the toes during a single gait cycle, can be also assessed.

There is also the possibility to view the pressures developing sequentially from the heel strike to toe-off in a three-dimensional mode, which shows the pressures as peaks acting on the sensor at each moment in time. This can find use as an explanatory tool in the education of patients.

Terminology

When describing values of plantar pressure recorded, clinical significance is placed upon the highest value of pressure measured. In this thesis, strict definitions of the terms "peak" and "maximum" are adopted to provide clarity with respect to spatial and temporal factors.

When looking at a snapshot of the pressure distribution beneath the foot at one instant in time (spatial analysis) there may be several discrete areas of ***peak*** pressure evident at that particular moment.

When pressure is recorded at discrete locations beneath the foot against a timebase (temporal analysis) there will be a ***maximum*** value of pressure registered at each location, which describes the highest value observed in the time period.

3.3. Validation of F-Scan methodology in laboratory conditions

Time-dependent behaviour of the F-Scan plantar pressure measurement insole

3.3.1 Introduction

The F-Scan system is a relatively new method for dynamic in-shoe foot pressure measurement which accompanies a software for gait analysis. The foot pressure assessment is based on the principle of a force-sensitive resistor, which provides a high resolution of measurement. The sensor is thin and unobtrusive in the shoe, the sampling rate (1-100Hz) is adequate for most clinical applications and the software is user friendly **(Woodburn and Helliwell, 1996)**. Good reproducibility was reported in a study of static and dynamic foot pressures measurements by Rose et al. **(Rose et al., 1992)**. Fergusson-Pell and Cardi **(1993)** have demonstrated a high degree of linearity: coefficient of linear regression >0.99, although in the presence of creep (calculated as a percentage of the initial reading: 7.5% at 2 minutes and 13.5% at 10 minutes of 100mmHg applied pressure) and hysteretic (calculated as the maximal difference in average measured pressure as a percentage of the applied pressure at the point of maximal difference: 22%) effects for the seating sensor.

Therefore the technology is known to suffer from a number of drawbacks which are inherent in the polymeric inks used to lay down the printed circuit which forms the sensitive matrix. Rose et al. **(1992)** also indicated that calibration between separate sensors was poor and that sensor pads showed significant wear with use.

Furthermore the variability of both F-Scan and EMED insoles was assessed by McPoil et al. **(McPoil et al., 1995)**, through a series of bench tests in which known pressures were applied using a rubber bladder filled with compressed air. When the pressure was repeatedly applied, the measured pressure versus known pressure showed a linear behaviour in both insoles, though with larger variability in the F-Scan insole. The average error at 50kPa was 16% for EMED, and 4% for F-Scan and at 500kPa, it was 0.8% for EMED and 24% for F-Scan. When a continual load of 150kPa was applied, the creep, which is the ability of the material used in the manufacture of insoles to resist change under an applied load over time, was found to be <3.4% and had a linear pattern for EMED, whereas the total creep for F-Scan was 11.6% and the pattern of creep did

not appear to be linear. When the F-Scan calibration was tested with an electromechanical testing machine (Instron 4505) by applying a known load and taking the output from the F-Scan system, the results showed a variability of 0-50% of pressure values between sensing cells. They also found a sensitivity of ±5kPa using static calibration, with day-to-day variability and test-to-test variability (10-20kPa for each cell and 4-100kPa between cells). The authors suggested as a solution to this problem to take an average pressure value of a number of elements which produce lower pressure values. **(Nikolopoulos, 1996)**. Recent Tekscan reports on the new ink developed by them, have shown an improved cell-to cell variability of <5% if the sensor is calibrated prior to use and tested with the averaging option activated.

3.3.2 Rationale and aims for the validation studies

Considering that the F-Scan system was intended for clinical research and practice, these accounts of numerous impediments in the use of F-Scan highlighted the necessity for assessment of the technical characteristics of the insole and for validation of the version of F-Scan system in use in the Diabetic Foot Clinic at King's College Hospital. This version uses an improved software and the latest F-Scan insole, manufactured with a new conductive ink supposed to reduce creep and hysteresis. Thus it was aimed to test the insoles initially in laboratory conditions in order to characterise a number of aspects, particularly cell-to-cell variability, threshold, temperature sensitivity, sensitivity to bending, alleged initial 'bedding-in' and creep behaviour. Then a validation study in clinical conditions was planned in order to allow the development of a methodology for the use of F-Scan with reduced variability and increased reliability.

Aim of the laboratory validation study

The aim of the study was to evaluate the initial bedding-in and longer term time-dependent behaviour under cyclical loading. Pressures have previously been recorded for the seating sensor (Tekscan "Seat"), and showed an increase of 8-18% after 2 minutes of steady loading, and 13.5-26% after 10 minutes, dependent on loading level **(Ferguson-Pell and Cardi, 1993)**. This study has been performed to increase awareness of the behaviour of the system in order to allow selection of optimised calibration and trial procedures. This may help maximise the usefulness of this technology.

3.3.3 Method for creep tests

F-SCAN system as described in the previous subchapter.

Testing methodology

The F-Scan insole is manufactured by sandwiching a printed circuit of force-sensitive resistive (FSR) material between two layers of Mylar substrate. The full-size insole (US men's size 14) consists of 960 pressure square cells spaced 5mm apart and evenly distributed in a grid-like configuration. Each cell acts as a force measuring device, the system software calculates the average pressure on each cell based on the measured vertical load and the cell area.

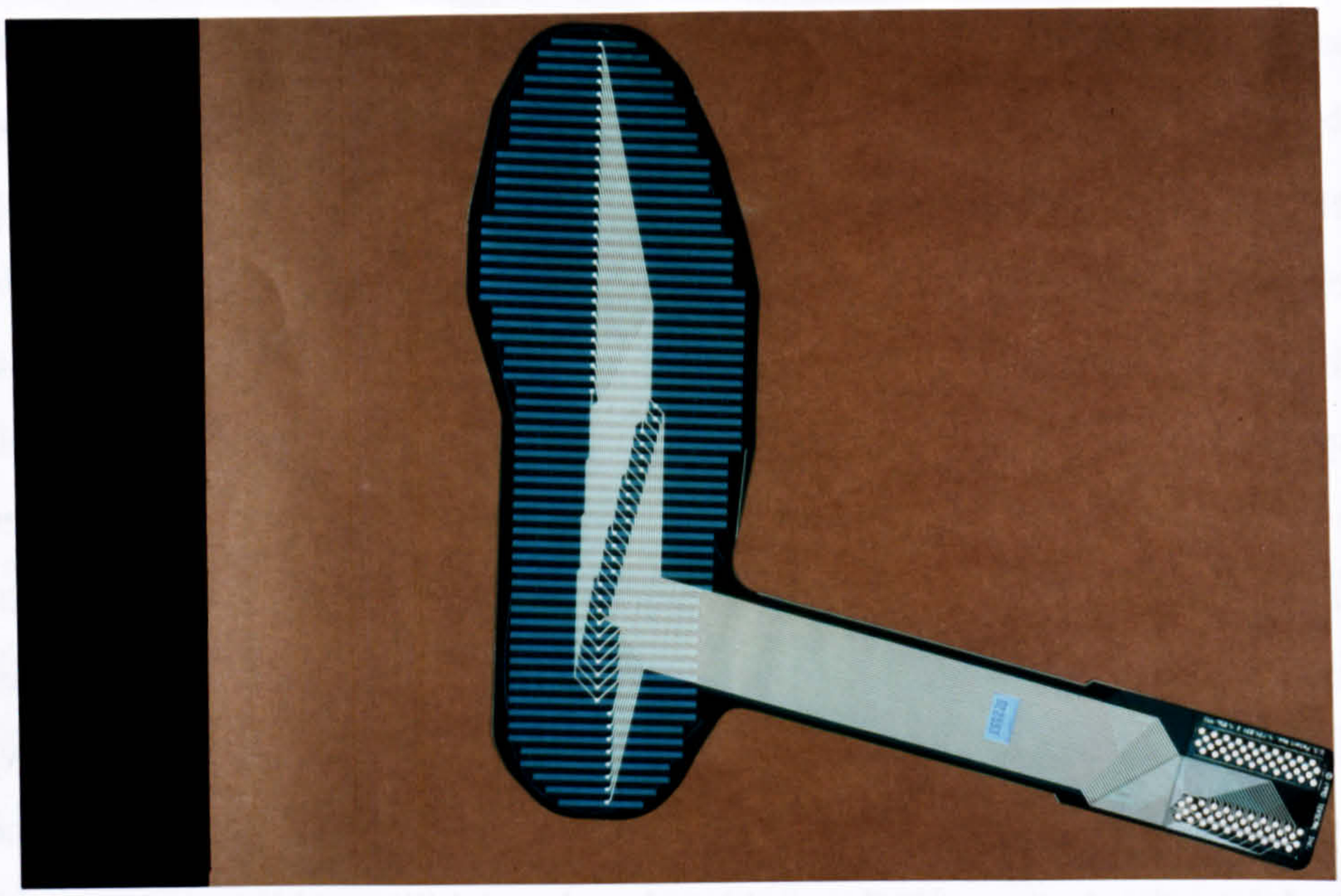


Fig. 3.3.1 F-Scan insole

An Instron model 1195 applied loads to the pressure sensitive insole, which was placed between two metal rectangular plates (310 mm x 120 mm).

An additional layer (3 mm thick) of foam with small even pores, which is normally used in the manufacture of bespoke shoes, was inserted under the F-Scan insole for the following reasons:

1. to spread the load, which is applied by the Instron plates in an uneven manner on a micro-scale: without the foam typically a mix of point and line contacts are seen. The foam provides additional compliance by producing local spatial redistribution.

2. Also in clinic, the insole would not be sandwiched between metal plates but between the soft tissues of the foot and the shoe insole. Thus the foam was also added to mimic as far as possible in this laboratory experiment, the in-shoe conditions. Unless the pressure is evenly distributed across each cell, errors will be introduced.

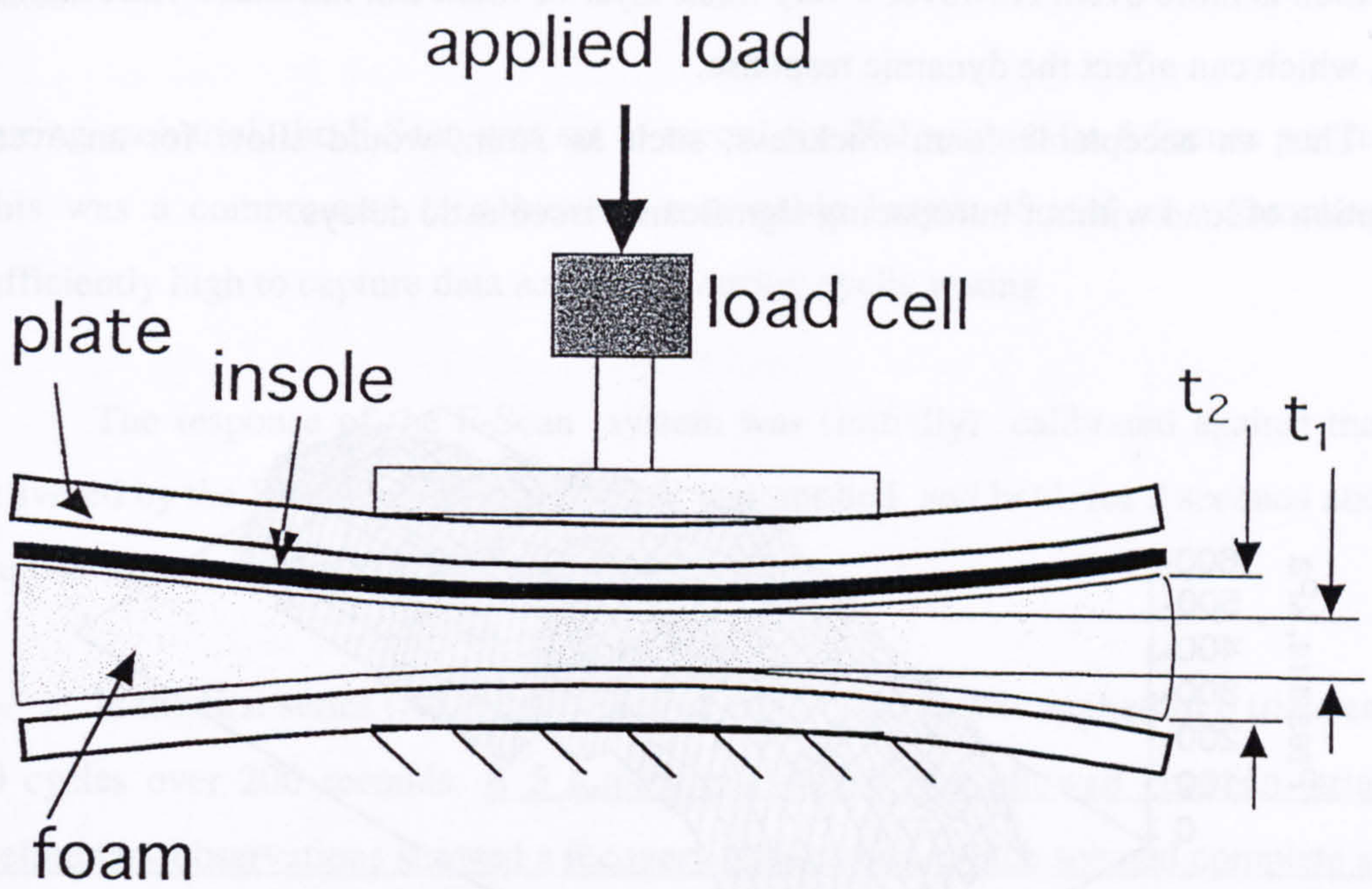


Fig. 3.3.2 The F-Scan insole and an additional layer of foam were placed between the two plates of the Instron machine

3. the thickness (3mm) of the foam allowed redistribution of pressure without adding a significant movement of the Instron when compressing the foam. This movement could lead to notable delays in application of load by the Instron, if the foam is thicker.

4. in order to mimic the pressure (cca. 200 kPa) developed under the foot in a good orthopaedic shoe, a high force (cca 6000N) has to be applied over an insole of approximately 300 cm^2. When this high force is applied, the Instron plates despite their rigid construction, bend at the outer edges resulting in an uneven pressure distribution falling off from the central area towards the edges.

In theory, with a layer of foam inserted, the variation in pressure from centre to edges is approximately proportional to $(t_2 - t_1)/t_0$, where t_0 is the original thickness of the foam and t1, t2 are defined in Figure 3.3.2. With an even pressure distribution, plate

deflection will be solely determined by its stiffness, and hence (t_2 - t_1) is fixed; this condition of zero pressure variation can therefore only theoretically occur as $t_0=\infty$. Hence inserting a thicker layer of foam causes the deflection of the plates at the edges to become less significant compared to the plate travel and the resultant pressure distribution is more even. However a very thick layer of foam can introduce viscoelastic delays, which can affect the dynamic response.

Thus an acceptable foam thickness, such as 3mm, would allow for an even distribution of load without introducing significant viscoelastic delays.

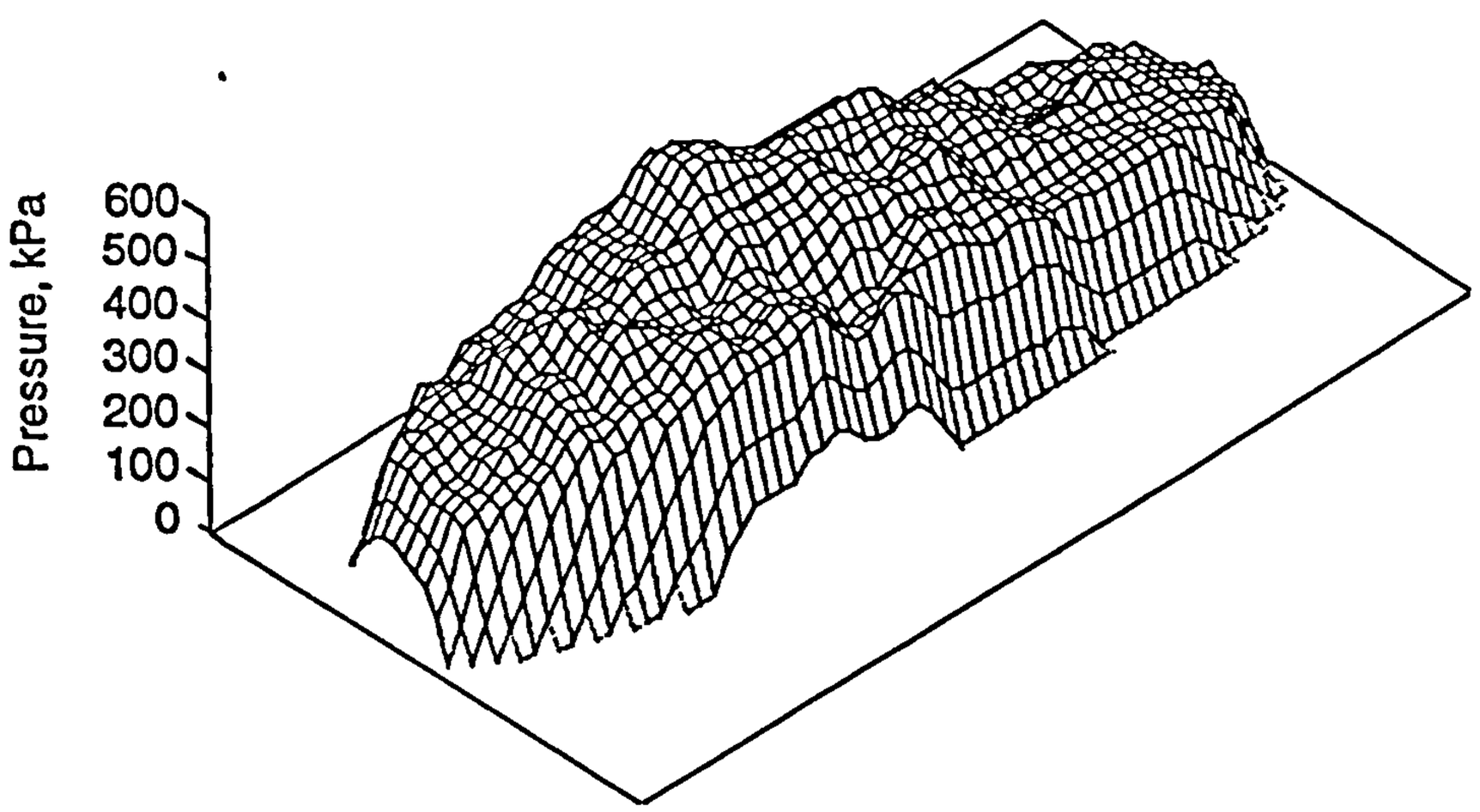


Fig. 3.3.3. Tridimensional representation of the F-Scan recording of pressures

In cyclical tests, the plates were driven by a ramp displacement with reversal at a preset load; ramp velocity was varied to control the cycle time. Figure 3.3.3 shows a three dimensional representation of the F-Scan recording of pressures, achieved with a 3 mm layer of foam and a ramp velocity of 20 mm/minute between loads of 100 N and 6400 N.

In cyclical tests any creep behaviour of the insole could be a function of time or related to the number of cycles: to discriminate this the ramp velocity of the Instron was increased in some tests to 50 mm/minute.

For static tests, a constant load of 3100 N was maintained this resulted in small oscillations of about 20 N around the set load level as the Instron periodically took up compression of the foam to maintain the required load.

Procedure

A single layer of closed cell foam of thickness 3 mm was cut to the size of the F-Scan insole. A new insole was then laid onto the foam and placed between the loading plates.

During each trial, the F-Scan was set to record for 200 seconds at 5 frames per second. This was a compromise to achieve a reasonable length of trial at a sampling rate sufficiently high to capture data accurately during cyclic testing

The response of the F-Scan system was (initially) calibrated against the load delivered by the Instron. A load of 5500 N was applied and held for 2 seconds and then the F-Scan response was scaled against the load.

In the first series (A), a load cycle of 100 - 6400 N was applied in 6 trials each of 20 cycles over 200 seconds. A 5 minute rest period was allowed between trials, as preliminary observations showed a recovery phenomena, which seemed complete after 5 minutes. In the last two trials, A7 and A8, the ramp velocity was increased from 20 to 50 mm/minute, with the same cyclic load. The F-Scan rate of sampling was kept the same in A7 trial as in A1-6 at 5 frames per second for A7, but in A8 trial the rate of sampling was doubled (10 frames per second, for 100 seconds, for better time resolution.

Another series of trials (B) were performed as for (A) but with the addition of a thermocouple to monitor the temperature at the interface between the insole and foam. In the first B trial (B1), the Instron was set as for A1-6 series; in the second B trial (B2) the Instron was set to apply double the load at double the frequency. A model H400 Digital Thermometer (Hale Instruments Ltd., Cheshire, UK) with a miniature thermocouple was used to monitor temperature resolution of 0.1 °C and accuracy 0.5 °C.

In the final series of trials (series C), a steady load of 3100N was maintained for each 200 seconds trial period. The recovery period was again 5 minutes. Care was taken to start each series A and C, with a completely new insole. The insole used in series B had undergone a number of trial cycles prior to the series.

F-Scan pressure analysis

In all trials, pressure analysis was done with the F-Scan 'Average' function to reduce cell-to-cell variability; this function averages across any adjacent 3 by 3 matrix of cells. Pressures were displayed against time and the 'Peak' function selected the highest pressure recorded in any specified loading cycle.

3.3.4 Results

Cyclical load trial

An example F-Scan graph of pressure against time for a single trial in the A series (A3) is shown in Figure 3.3.4. There is an upward drift in apparent peak of pressure in each cycle.

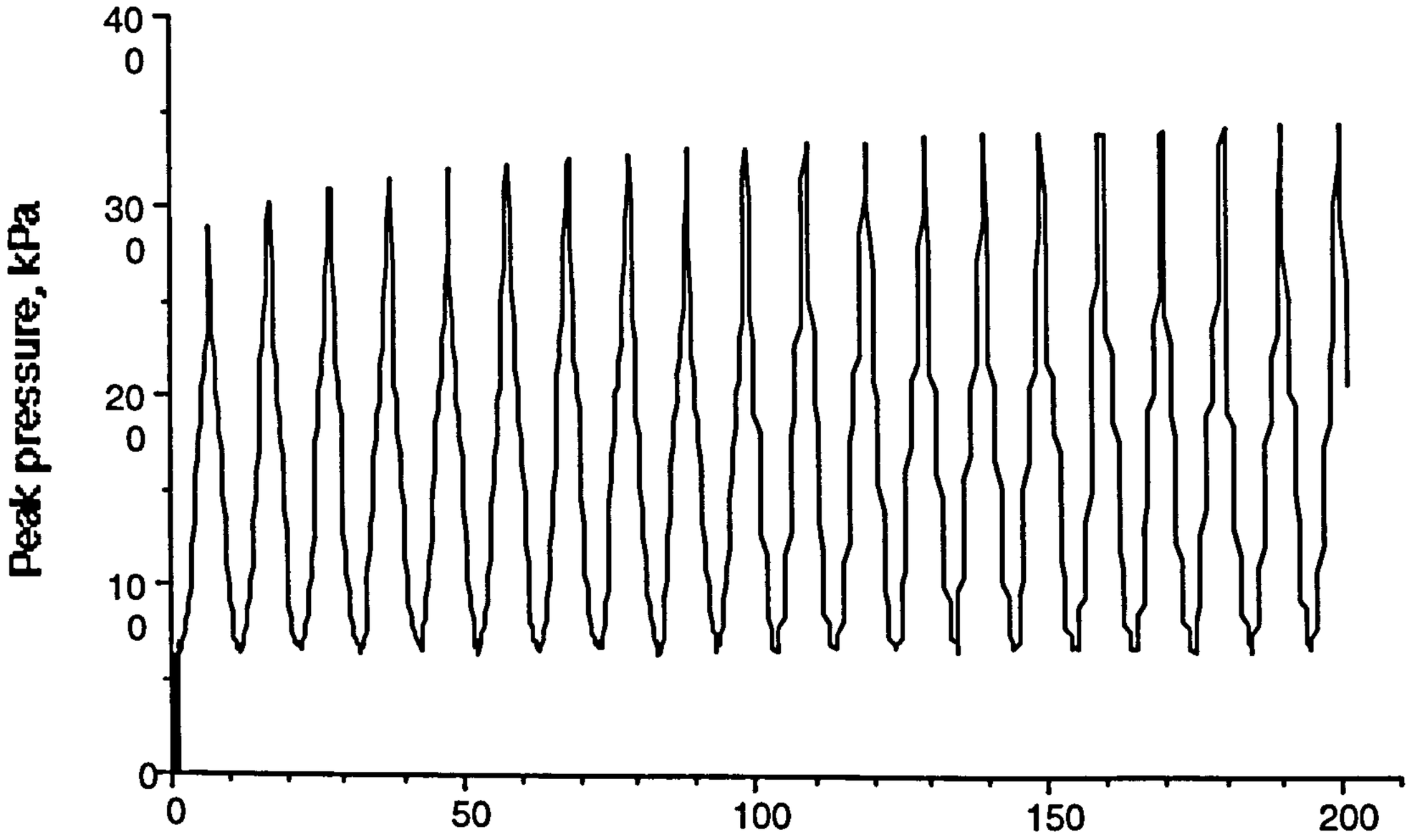


Fig. 3.3.4 Loading profile recorded from F-Scan in cyclical loading

In every trial, peak pressure rose during the 20 cycles: e.g. for series A, trial 3, the initial and final peak pressure readings were 272kPa and 316kPa respectively.

The mean increase for the first six trials in series A was: 14.7±2.1 (9.4-23.5)% from the first to the last peak; and respectively 8.5±1.7% when measured in the first peak after 30 seconds versus the last peak.

In the fast speed trials A7-A8, the mean increase in measured pressures from the first to the last peak was 12.8±2.9(9.9-15.7)% and 4.3± 2.2 (2.1-6.6)% from the first peak after 30 seconds to the last peak.

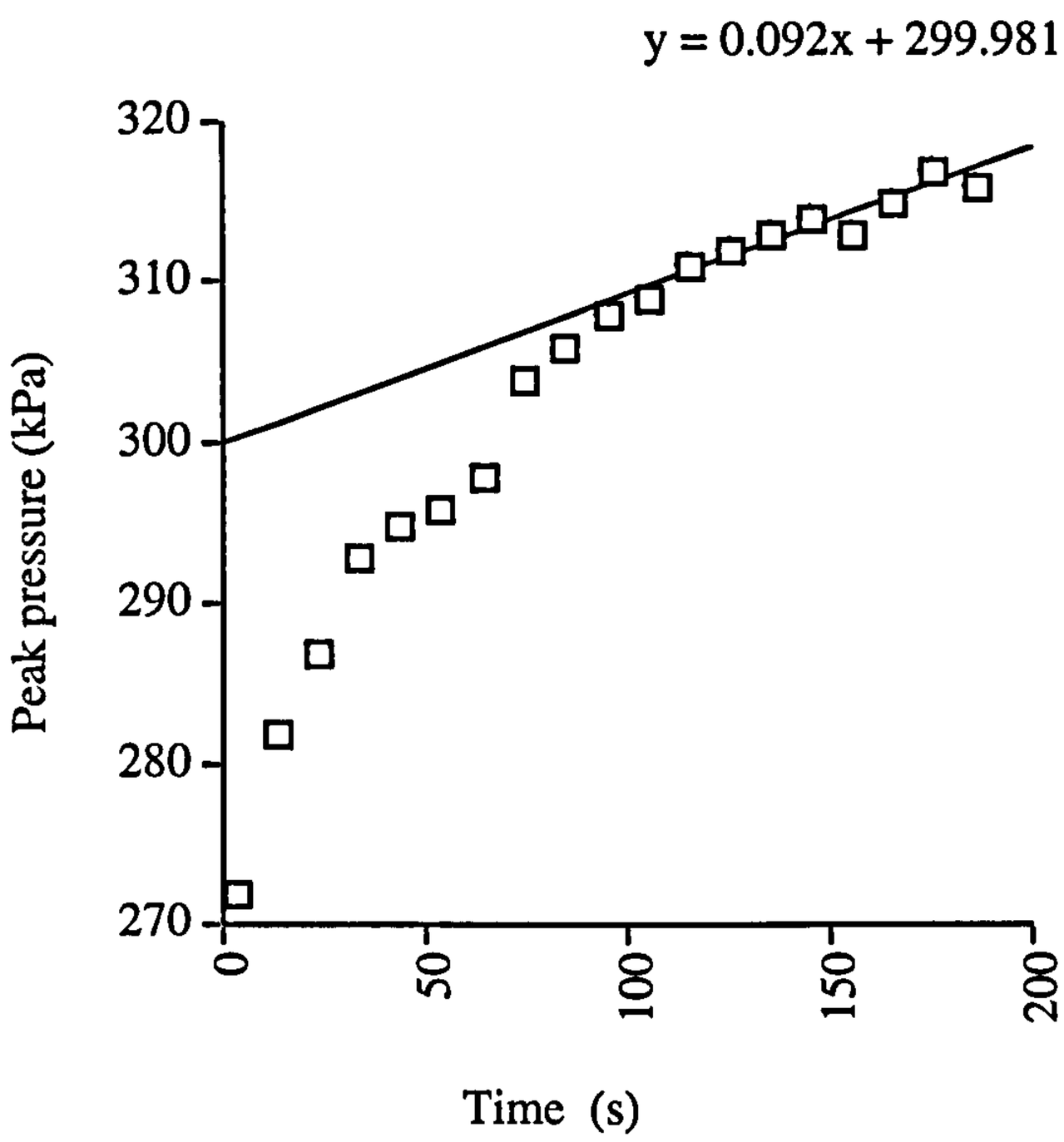


Fig. 3.3.5 Example plot of peak pressure per cycle; after an initial rapid rise, the plot is approximately asymptotic to a straight line

An asymptote was determined for this latter part of the curve, as shown in Figure 3.3.5. The rise period for the first rapid phase of the curve was estimated, taken to where the curve joined the asymptote. Accuracy of rise periods is ± 5 seconds (i.e. one half cycle).

Trials conducted at the slower cycling rate (A1-A6 at 0.1 Hz) gave a mean rapid rise period of 74±6 (62-84) seconds: this can be compared to a rapid rise at the faster cycling speed (A7-A8 at 0.25 Hz) of 58-59 seconds. In terms of cycles, rapid rise periods were 8±1(7-9) cycles at the slower frequency and 14-15 cycles for the tests at higher frequency.

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Steady load trial

For comparison, in the steady load trial pressures measured at 30 sec were taken as the first measurement, to avoid recording the transients during application of loading. The last pressure measurement was at 180 seconds. The mean increase for the six trials in series C was 7.3±2.6 (3.0-20.4)%.The increase in the cyclical peak pressure can be described as a more rapid rise occurring within the first 80 seconds, followed by a slower rise over the remainder of the trial.

Effects during the series of trials

The gradient of peak pressure rise against time was calculated (Figure 3.3.6). A decrease in the gradient was found progressively from A1 to A6 suggesting that this characteristic reduces with continual use.

The changes in cyclical peak pressures during series A, both from the first to the last cycle of each individual trial and of the variation from trial to trial, are represented graphically in Figure 3.3.7. It can be noted that recovery occurs between each trial and that the baseline of the initial pressure reading is not constant, but tending to increase over the series.

In the first B trial (B1) the temperature recorded at the beginning of the trial was 21.2 °C and after the last cycle the temperature rose to 21.3 °C; in B2 trial when both the load and ramp velocity of the Instron were increased, the rise in temperature was just 0.2 °C from 21.2 to 21.4 °C.

Fig. 3.3.6 Gradient of the asymptote to the later response

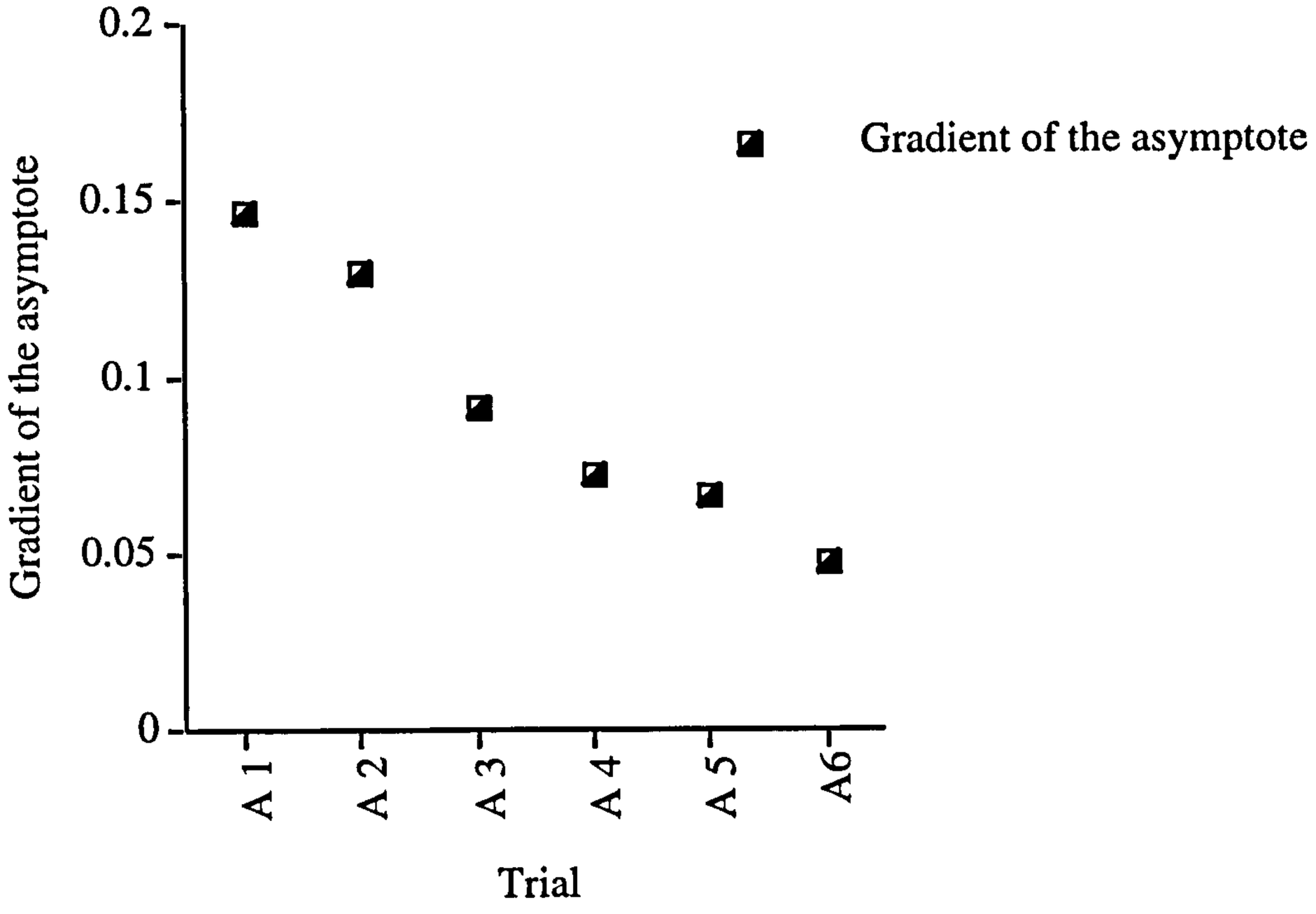
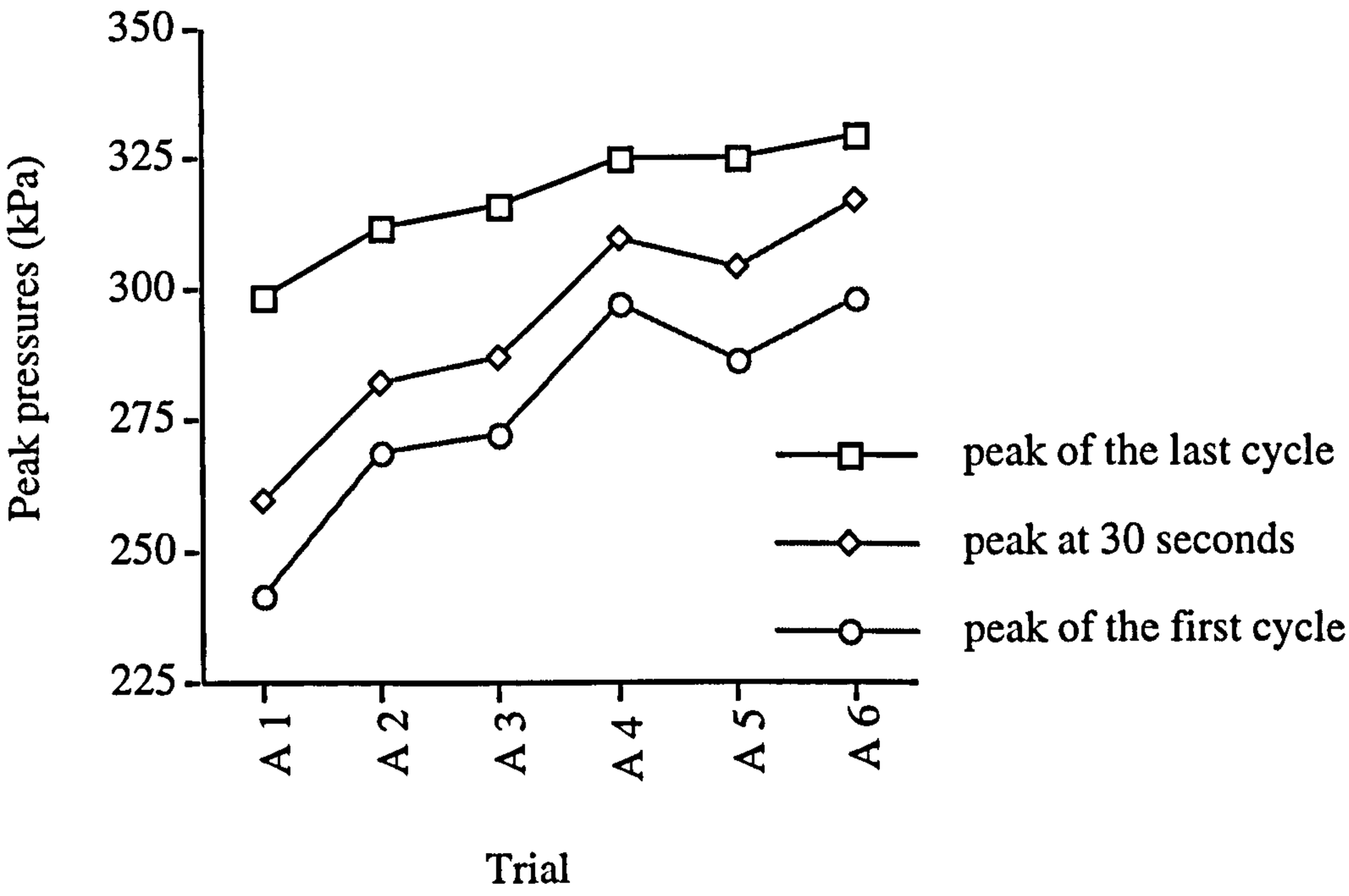


Fig. 3.3.7 Peak pressures recorded from the first-last cycle



3.3.5 Discussion

As expected, appreciable time-dependency has been demonstrated in F-Scan response to cyclical and sustained loading, in the form of increasing sensitivity to pressure over the course of the each trial. This continuation in change of sensitivity beyond 2 minutes has been observed earlier by Fergusson-Pell and Cardi **(1993)**. The magnitude of the rise over 200 s trial varied considerably, for example from 9% - 24%, mean 15% in the first six trials in Series A.

Two elements of this increased sensitivity can be observed: a rapid rise at the commencement of loading, and a more gradual steady increase over a period of several minutes. During cyclical loading, the rapid rise is substantially completed in approximately 70 seconds- 90 seconds, this representing 7-9 cycles (figure 3.3.5) at the lower test frequency and 14-15 cycles at the higher frequency (utilised). This element of the response is therefore primarily sensitive to time under load and not the number of loading cycles. After the initial rapid rise, the response becomes approximately asymptotic to a straight line of positive slope over the remaining period of each trial. By plotting the gradients of these slopes over a series of trials, Figure 3.3.6, it can be observed that the slow increase gradually diminishes as the sequence of trials proceed.

The increase in sensitivity appears to be largely recoverable between each trial following a rest of 5 minutes, Figure 3.3.7. However, there is an upward drift in the sensitivity with repetitive trials during a series, evidenced by the gradual rise in the starting and finishing peak pressure values. This represents an irrecoverable component in the response or a component which only recovers over a much longer time scale than the rest period.

The curve of the starting peak pressure values in Figure 3.3.7 show that the irrecoverable increase is levelling out by the sixth trial, indicative of some initial creep-like or bedding-in phenomena which reaches a maximum value. Similarly the curve of slope gradient against trial number is also levelling out, Figure 3.3.6. This suggests an association between the slower steady increase and the irrecoverable component. It is proposed that the slower element of the sensitivity increase gives a permanent set due to creep-like behaviour which is complete over the first 20 minutes of loading (6 trials of

200 seconds); whereas the rapid element is recoverable, due to viscoelastic properties and occurs repeatedly in the first 80 seconds of loading following a rest period.

It has been suggested previously that a new insole would show an initial change in sensitivity as flattening of the surface asperities of the ink induce lower resistance across each load cell. The results from these present trials, each commencing with a new insole, do not show evidence of this in the first trial as expected, but this could reasonably be proposed as the mechanism responsible for the slower irrecoverable creep-like component in the response.

A comparison can be made between cyclical and static trials responses. In static tests, it was not possible to determine the rapid rise accurately; on this particular Instron, it took up to 30 seconds to apply the static load gradually under manual control. Hence for purposes of comparison to the increases during cyclical tests, the recorded pressures were registered at 30 seconds and 180 seconds in static tests. The mean increase in the six trials in series C was 7.3%, range 3.0%-20.4%. This is approximately half the increase found in the cyclical tests from first to last peak, but corresponds to the mean increase of 8.5 (3.7-15.0)% found from the first peak occurring after 30 seconds to the last peak. This again indicates that it is primarily the duration of loading and not the cyclical nature of the loading, which is responsible for the observed behaviour.

In order to eliminate two possible explanations for the observations, we also recorded the temperature rise and the Instron loading profile during a series of trials. The F-Scan manufacturer reports temperature sensitivity of this particular ink to be 1.8% per1°C, and hence the temperature increase recorded (0.2 °C) is insignificant. From the Instron force profiles, a small increase in loading magnitude can be observed at the start of a cyclical trial: this is due to initial compression of the visco-elastic foam inserted under the insole, which then allows higher forces to develop between the plates. However the rise occurs over the first two or three cycles and is also small, less than 2%.

From the point of view of the significance of these results to calibration of the F-Scan during clinical trials, we first note that the recommended life of an insole is 10 walking trials. After this, rapid deterioration in the transducer response due to delamination from shear may render the insole unusable: such deterioration was not

noted in our trials where only vertical loading was applied. A calibration procedure must be appropriate to this expected life. Also because of the temperature sensitivity of the insole, care must also be taken to achieve equilibration with the foot in-shoe temperature before trials commence.

The findings indicate that it is necessary to walk the patient on an insole for at least 60-90 seconds to overcome the initial rapid rise, after which the calibration against bodyweight and the trial walk should take place immediately. If the patient rests between walks, recovery will occur, and so a further 60 seconds of loading is necessary before each trial. The manufacturers recommendation for 'bedding-in' an insole is supported for this reason, although it is noted from these experiments that this is not a one-off requirement.

It is not practicable to overcome all the slower creep-like response by walking, since the 20 minutes required would frequently induce delamination: it might be possible to pre-condition the insoles with a static vertical load, although further research would be necessary to determine any longer-term effect of this treatment on 'shelf life'. Notwithstanding, it would be beneficial for the patient to walk for several minutes on a new insole which will overcome a substantial part of the anticipated creep.

Conclusion

From these trials, it is suggested that there are two elements in the observed increase in sensitivity of this FSR insole transducer during loading. The rapid element demands that that the insole be conditioned by at least 60 seconds of loading prior to calibration, and that a trial walk be undertaken within a few seconds thereafter. Because of a permanent creep-like element of the response, sensitivity will continue to change slowly over several minutes even after the initial rapid rise is finished. This necessitates calibration at frequent intervals.

3.4 Validation of a clinical methodology for in-shoe pressure measurement using F-SCAN

3.4.1 Background

An accurate device to measure plantar pressures under the foot would play an important role in the diagnosis and treatment of foot conditions.

Most of the previously reported studies of plantar pressures have measured a limited number of isolated, barefoot steps in a laboratory setting **(Lord et al., 1986; Cavanagh et al., 1985).** Such isolated snapshots of barefoot plantar pressures did not give us insight into possible step-to-step variations or information about plantar pressures which occur when wearing shoes, but it is also important to measure the peak plantar pressures within the shoe during normal walking conditions **(Lord and Hosein, 1994)**. In-shoe forces which occur during walking have not been well described, because standardised methods of in-shoe foot pressure measurement have not been developed until recently. Different types of equipment for in-shoe foot pressures measurement have different technical characteristics: the earlier discrete devices were able to detect pressures only under the area where they were placed and often they would be displaced due to the shear forces developed inside the shoe. Several systems using a matrix insole for in-shoe measurement of plantar pressure are now commercially available. They have enabled researchers to make clinical investigations **(Pitei et al., 1995; Corbett et al., 1993)** which were hitherto impracticable. Only a few studies have examined quantitatively in-shoe plantar pressures, using different systems of in-shoe foot pressure measurement during continuous walking by normal sensate control subjects and diabetic patients with neuropathy. In recent years, the two most used systems for in-shoe foot pressure measurement have been: the EMED system (Novel Gmbh, Munich, Germany) which uses a capacitance transducer and the F-Scan system (Tekscan Inc., Boston, MA) which uses a force-sensing resistor.

Clinical comparisons were attempted to provide more information regarding the reliability of different types of foot pressure devices. When the F-Scan was compared to the Dynamic Pedobarograph (DPBG) (in one patient wearing the F-Scan insole attached to his foot while he was walking on a DPBG platform), it was interesting to note that the pressure pattern of the different anatomical points was identical in the two systems and the range of pressure was similar, with small intra-subject pressure

variability **(Nikolopoulos, 1996)**. However the author also described a 'preconditioning' effect stabilised after the initial ten cycles with the F-Scan insole. In comparison with the platform systems of foot pressure measurement, which are reliable, but do not allow assessment of forces developed inside the shoe, the in-shoe insole devices are ideal for characterising the forces at the shoe-foot interface, but they have certain technical problems as regards reliability. In-shoe pressure measurement raises potential problems because the sensor has to acclimatise to the in-shoe conditions of temperature, moisture, shape and size of the shoe which will influence the pattern of loading of the vertical forces due to body weight as well as the shear forces expressed when the foot slips inside the shoe.

Furthermore the F-Scan was compared to the EMED system in a dynamic study in four healthy subjects **(McPoil et al., 1995)**. The F-Scan insole was found to have a good to fair level of reliability between different days of testing, different trials, different steps for the first peak of force during the contact phase of the stance, whereas the reliability was found to be poor for the propulsive phase of the stance. However the EMED reliability proved to be good over all the stance phases. However they were able to measure only forces, not pressures because the spatial resolution is much higher in the F-Scan insole with its 966 FSR sensors, than in the EMED insole with its 99 capacitance transducers **(Cobb and Clermont, 1995)**.

Also the F-Scan insole is ultrathin (0.16mm), flexible and can be trimmed to the size and shape required to fit the footwear. In comparison the EMED insole is rigid, is 2mm thick and comes in standard sizes and shape. However the F-Scan insole is disposable and therefore it has a limited life-time, whereas the EMED insole is supposed to last for longer and is also much more expensive. Also the recording parameters such as sample rate, analysis time, number of frames, can be adjusted through the software facilities to suit the characteristics of the experiment and sometimes may account for different results found with different systems.

Therefore the differences in the technical characteristics of the various equipment could influence the results and the comparisons made between them. They also seem to recommend different systems for different roles in the diabetic foot care: the EMED would be suitable as a screening device due to its reliability, whereas the F-Scan which benefits from a high spatial resolution and adjustability, seems to be more appropriate for the assessment of therapeutic measures for plantar pressure reduction, such as chiropodial treatment and prescription footwear for the diabetic foot.

However in order to use the F-Scan system, which was still in prototype stage when it arrived in the laboratory of the Medical Engineering and Physics Department, King's College Hospital, for clinical research or practice in the Diabetic Foot Clinic, its technical limitations needed addressing in order to validate and standardise a reliable method of plantar pressures assessment.

The technical characteristics of the F-Scan sensor obtained in laboratory conditions of repetitive loading (imitating the normal gait) and details of the behaviour of the insole in these circumstances are described in the previous subchapter. The conclusions drawn would help improve the calibration procedure and the accommodation of the insole inside the shoe to overcome a substantial part of the anticipated creep. However these tests were done in laboratory conditions when a constant vertical load was repeatedly and evenly applied. In the clinical setting, the real-life conditions inside the shoe in which the F-Scan insole is to be used, are very different. It means putting the insole in contact with curved and uneven contours, especially in a diabetic foot characterised by deformity which would develop high pressures under certain areas whether other areas would not be loaded at all. Also placing the insole in the shoe and taking it out will induce a degree of manipulation, which might affect its longevity. Likewise the conditions of humidity and temperature developed inside the various shoes of various groups of patients may have a different effect on the behaviour of the insole. All these variables plus the variables introduced by walking such as, step-to-step and test-to-test variability need assessing in a clinical setting in order to minimise the deficiencies and develop a valid methodology for foot pressure measurements with suitable accuracy and reproducibility.

Aims of the clinical validation study

The aim of our study was to develop an optimal clinical procedure in order to obtain reproducible results with the F-Scan taking in consideration its technical limitations.

The clinical validation study was designed in two parts:

1. methodological studies of the characteristics of the F-Scan insole inside the shoe in order to acquire validation of the research studies for clinical practice. The reliability of the insole in consecutive runs, the life-time of the insole and the temperature change inside the shoe during a F-Scan test were studied.

2. a clinical pilot-trial, whose aim was to validate the F-Scan technique recommended by the previous methodological experiments, in a clinical setting involving two groups of patients: diabetic patients with neuropathy and a history of foot ulceration and non-diabetic controls.

The diagnosis of these two groups is only relevant because they represent likely clinical conditions of diabetic neuropathic patients with insensate feet, who have a high risk of developing foot ulceration. The methodology was particularly aimed at neuropathic diabetic patients with insensate feet which can interfere with the behaviour of the F-Scan insole by creasing it and thus reducing its life-time. Also the sensitivity of the insole to the in-shoe conditions of temperature and humidity can be different when in contact with a neuropathic foot, which is characterised by higher plantar pressures and higher skin temperature, but less moisture due to sympathetic denervation manifested as a decrease in sweat secretion. Also abnormal shape due to deformity, claw toes and Charcot joint could be present in the neuropathic foot and potentially increase the degree of manipulation of the F-Scan insole, reducing its durability. A control group was included in the study, in order to observe any differences in the behaviour of the insole. The variability between runs, the inter-step variability and the reproducibility tests were assessed.

Methods and patients

Two groups of subjects were studied. They were known from previous work **(Boulton et al., 1987)** to be characterised by significantly different ranges of pressure:

Group A: 11 neuropathic patients with a previous history of foot ulceration, no history of intermittent claudication and foot pulses palpable bilaterally. Neuropathy was defined by the presence of neuropathic symptoms and the absence of ankle reflexes accompanied by abnormal vibration perception threshold (VPT>20 Volts) measured from the tip of the great toe using a Biothesiometer (Biomedical Instruments, Newbury, Ohio, USA) **(Guy et al., 1985)**. This test was performed six times and the mean value was calculated. Vibration perception is a function of large myelinated fibres, which may be damaged at a later stage in the neuropathic process than the smaller fibres conveying thermal sensation **(Guy et al., 1985)**.

Group B: 11 non-diabetic controls of whom none had a family history of diabetes.

Table 3.4.1 Clinical details of patients

	Non-diabetic control subjects	Diabetic neuropathic patients
Number	11	11
Age (years)	52.5±11.1	58.3±12.8
Sex	5M / 6F	6M / 5F
Diabetes duration (years)	-	18.0±10.4
Type of diabetes	-	2 IDDM / 9 NIDDM
VPT (Volts) Mean±SD	6.5±1.5	39.8±9.2

Measurement of foot pressures

As described in the previous subchapter.

Each subject used a new insole. Recording of a subject walking on a flat surface 4 metres long, at his/her normal speed is referred to as a 'run'. Subjects were tested in standard shoes (Clarks trainers 'Swing Low') to avoid variation of foot pressures with different types of footwear. They were also given standard nylon knee-high hold-ups because hosiery can also alter the foot pressures **(Rose et al., 1992; Veves et al., 1989)**.

Analysis of the recorded pressures was done with the 'Average' function on, in order to activate a smoothing effect on the immediate surrounding cells. Peak plantar pressures were measured as they are an accepted parameter to describe the pressures developed at shoe-foot interface **(Cavanagh et al., 1996).**

Statistical analysis

The analysis of variance for pressure was done considering the run, the step and the site where pressure was measured as main effects and their interactions were calculated. Data are presented as Mean ± SEM and where appropriate as median (range). Data were analysed using the paired Student's t-test to compare pressures measured in similar anatomical locations in neuropathic patients versus control subjects.

3.4.2 Reliability of the insole in consecutive runs

Procedure

The reliability of pressure readings was not known with continuos repeated runs. Therefore we investigated the behaviour of the insole with repeated runs, without any break between them, by observing variations and discrepancies in the recorded pressures in two patients each wearing the same insole during consecutive runs without any break.

Results

Peak pressures recorded indicate that the insole was liable to fail after the 4^{th} continuous run.

Fig.3.4.1 Reliability of the insole in consecutive runs

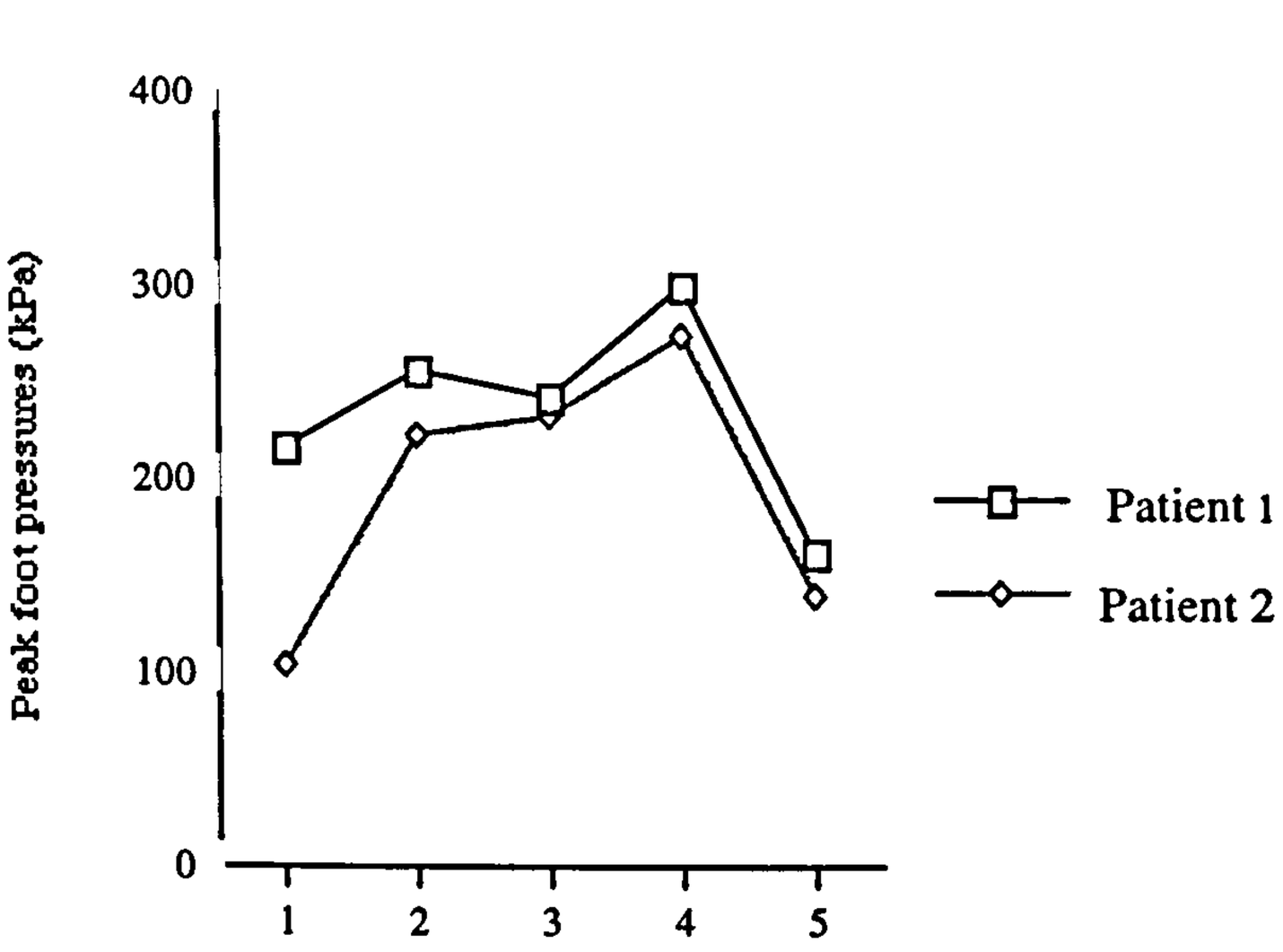


Table 3.4.2 Foot pressures (kPa) measured in continuos consecutive runs

Patient	1run	2run	3run	4 run	5 run
A	103	221	231	274	140
B	238	269	274	277	147

Therefore in order to avoid any interference it was decided that every test would consist of a maximum of 3 consecutive runs.

Furthermore, the very first run of a insole produced always a smaller reading than the subsequent ones suggesting that a "bedding-in" process was still happening.

Therefore the patients were asked to perform a first run on the insole without recording it, in order to allow them to acquaint themselves with the recording conditions and also to allow the "bedding in" process.

3.4.3.Life-time of the insole. Creasing and drop-out of the insole during non-consecutive runs

Procedure

The durability of the insole was not known and therefore it was uncertain as to the maximum number of runs each individual insole could be used without errors or artefacts.

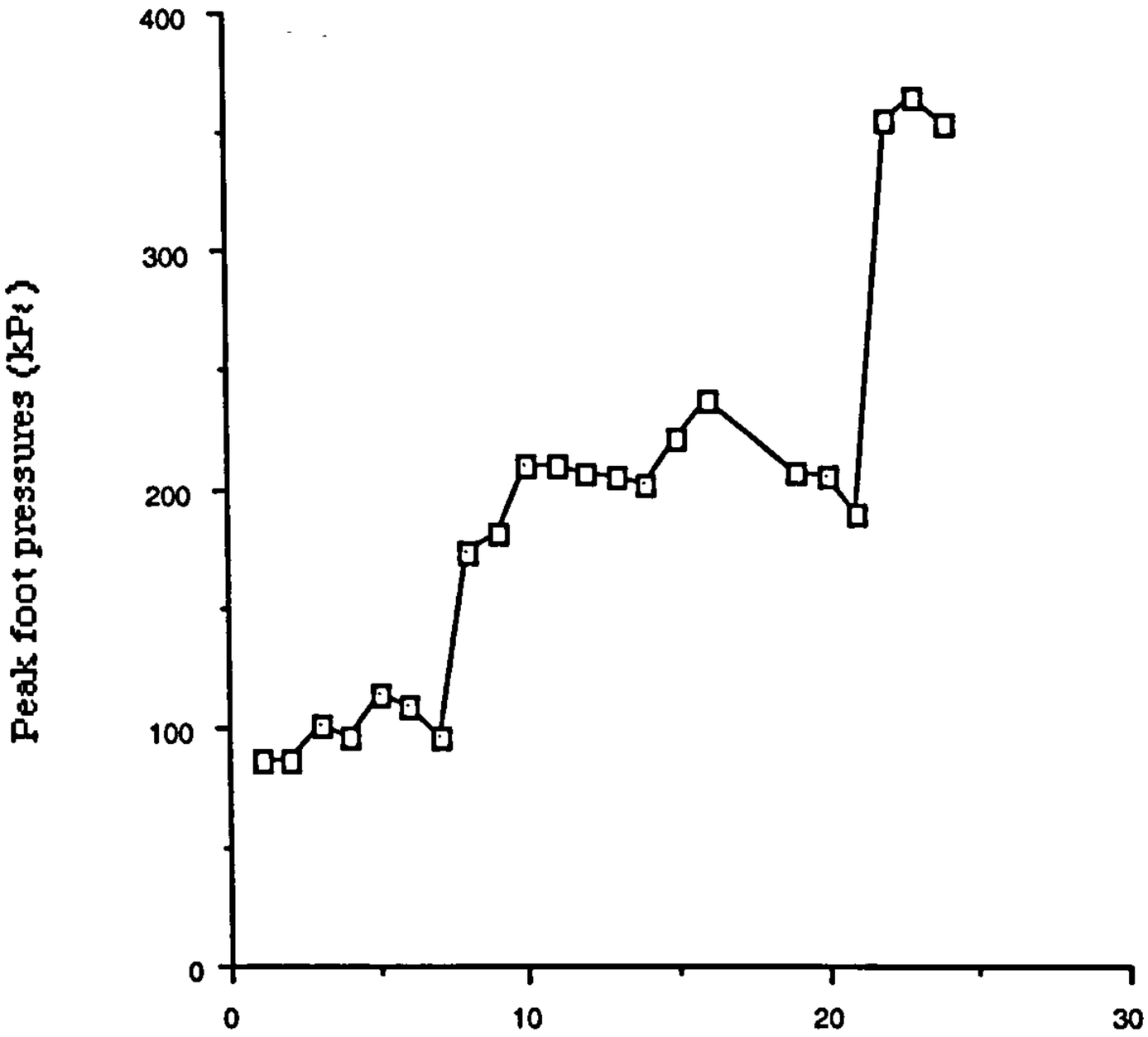
The life-time of the insole was assessed in 3 patients, each using a new insole, by repeating the measurements until failure of pressure readings was noted as shown by tracks missing on the screen corresponding to the areas of creasing of the insole.

The runs were carried out with breaks between them, when the insole was taken out from the shoe and then placed again inside the shoe, before the following run was started. This procedure imitated the clinical conditions which the insole undergoes, including manipulation both inside and out the shoe, which can induce the creasing of the insole.

Results

This test of insole durability was carried out in the 3 subjects and the results for one patient are shown in the Fig. 3.4.2.

Fig. 3.4.2 Life-time of an insole. Creasing and drop-out of the insole during non-consecutive runs



The insole failed after 24 runs. Results in the other two patients were similar, the insole having a mean life time of 25 ± 3 runs.

Therefore it is recommended to use one insole for less than 20 runs in total and ideally it is advisable to use one insole per patient, especially in longitudinal studies.

3.4.4 Variability between runs

Procedure

In all 11 patients of both the control group and diabetic neuropathic group the foot pressures were recorded in two runs and results from the first run were compared to those from the second run.

Results

There was no statistically significant difference between the pressures developed in the first run versus the second run neither in controls (p=0.83) or in neuropaths (p=0.42) (Table 3.4.3)

3.4.5 Inter-step variability

Procedure

Each run lasted for 4 seconds and at a F-Scan sampling rate of 5 frames/second, approximately 3-4 steps were recorded per run in each subject. Foot pressures measured in successive steps were compared.

Results

The pressures measured in each step of the same run did not differ significantly from step to step (p=0.18, in controls and p=0.73, in neuropaths) - see Table 3.4.3.

Table 3.4.3 Comparisons between the pressures measured in different runs and between the steps of the same run

	Non-diabetic control subjects	**Diabetic neuropathic patients**
RUN 1 vs RUN 2	141.7±25.3kPa vs 149±28.8 kPa p=0.83	296±19.9kPa vs 300.8±15.5kPa p=0.42
STEP 1 vs 2 vs 3	139.3±35.6kPa vs 146.3+31.4kPa vs 150.4±31.4kPa p=0.18	281.6+25.7kPa vs 307±19.3kPa vs 306.7±18.5kPa p=0.73

Mean ±SEM

Therefore any step of any run could be chosen for foot pressure analysis, but in order to standardise the procedure the use of the second step of the second run or the mean value of all steps of one run is recommended.

3.4.6 Reproducibility tests

Procedure

Reproducibility was assessed in every group by calculating the coefficient of variation of the peak foot pressures with repeated measurements.

The control subjects (n=2) were tested in the morning and then in the afternoon of the same day.

Then the measurements were repeated a day later in the morning.

A week later the same patients were asked to come back and foot pressures were measured once again.

The neuropathic patients (n=3) were tested in two separate occasions, at 4, 5 and 6 weeks interval.

Inter-observer variability in reading the values of the pressures on the screen of the computer was also assessed by asking 2 observers to make an independent analysis of the pressures measured in one patient.

Results

Reproducibility was assessed in every group by measuring the coefficient of variation of the peak foot pressures. The coefficient of variation (CV) was measured in the two control subjects in three separate occasions at different time intervals: in the morning versus afternoon the CV was 5.3 ± 1.5 %., at 1 day interval the CV was 12.4 ± 0.9 %; and at 1 week interval the CV was 10.3 ± 1.3 %.

The three neuropathic patients who were tested in two separate occasions at 5±0.5 weeks interval showed a coefficient of variation: CV=18.9±4.1%.

Inter-observer variability in reading the values of the pressures on the screen of the computer was also assessed: CV=1.4±0.3%

3.4.7 Temperature change inside the shoe during a F-Scan test

Procedure

The change in temperature was measured in one control subject during a routine F-Scan test. A model H400 Digital Thermometer (Hale Instruments Ltd., Cheshire, UK) with a miniature thermocouple was used to monitor temperature at the interface between the subject's foot and the insole, where was secured with sellotape. The thermometer was attached at the ankle of the subject when walking.

Results

The temperature measured initially inside the shoe was 28.6°C and after the F-Scan test comprising of three runs of three steps, the temperature inside the shoe was 29.7°C, resulting in an increase in temperature of 1.1°C.

3.4.8 Clinical pilot-trial assessing foot pressures in control subjects and diabetic neuropathic patients

Procedure

In order to investigate the location of the peak pressures of the foot, these were measured under the big toe and respectively under each metatarsal head. Also in order to characterise the pressure distribution under the main areas of the foot **(Rose et al., 1992),** pressures were evaluated under the medial and lateral side of the forefoot and under the heel..

The size of the box which defined the areas of interest was adjusted accordingly:

2.25 cm^2 for the big toe

1cm^2 for each metatarsal head ,

11.25 cm^2 for each side of the forefoot, which was thus divided in the medial and lateral forefoot

11.25 cm^2 for the heel.

Results

The foot pressures were significantly higher under the hallux and the first, second and fourth metatarsal head in the neuropathic patients than in control subjects (Table 3.4.4).

Table 3.4.4 Peak foot pressures (kPa) in control subjects and neuropathic patients

A R E A	CONTROLS	NEUROPATHS	
Big toe	162.8 ± 54.6	268.2 ± 52.9	p< 0.05
1 metatarsal head	253.6 ± 51.8	433.2 ± 90.0	p< 0.005
2 metatarsal head	226.8 ± 36.2	338.8 ± 65.0	p< 0.05
3 metatarsal head	269.8 ± 17.0	287.2 ±123.1	NS
4 metatarsal head	128.0 ± 46.6	208.8 ± 61.6	p< 0.05
5 metatarsal head	124.5 ± 13.4	150.1 ± 60.8	NS
Heel	271.4 ± 52.2	397.3 ± 220.2	NS
Medial forefoot	254.5 ± 18.9	386.0 ± 107.2	p< 0.01
Lateral forefoot	126.2 ± 28.1	179.5 ± 66.2	NS

MEAN±SD

When the pressures were measured under the main areas of the foot, the pressures were significantly elevated in neuropathic patients versus non-diabetic subjects under the medial side of the forefoot, but not under the lateral side of the forefoot or under the heel (Table 3.4.4).

3.5 Discussion

This technology to measure in-shoe foot pressures has been only recently developed and it has been important to investigate this method in detail with particular regard to the characteristics of the insole.

In this study we have established a method for measurement of in-shoe foot pressures in order to achieve acceptable reproducibility necessary for the study of foot pressures in clinical practice and the following technique is recommended:

Recommendations for the use of the F-Scan

If a new insole is used, the patient (wearing standard shoes and socks) will be asked to walk normally on a flat, even surface for 2 minutes in order to reach a suitable level of "bedding-in". If an insole had been used previously, the patient will be asked to walk only for 1 minute in order to acclimatise the insole to the in-shoe conditions.

Then the insole will be calibrated against each individual body weight by asking the patient to load all the body weight on one foot, whilst concomitantly on the screen the pressure is checked to be evenly distributed and then the 'Calibration' function is triggered.

Then the initial run will be done immediately. It is recommended that an F-Scan test consists of 3 runs. The initial run will be a learning one. The next two runs will be recorded. It is advisable not to record consecutively more than 3 runs in a patient.

Calibration again at the end of the F-Scan test is recommended to check for major artefacts in insole sensitivity.

It is not recommended to use an insole for more than 20 runs in total, especially if tracks are missing persistently on the screen. It would be advisable to use an insole per foot per patient, especially if longitudinal studies are to be done.

In the analysis of pressure, it is advisable that the second step of the second run or the mean of all the steps in a run to be considered in order to standardise the assessment of peak pressures.

Also it is advisable to keep constant the size of the window containing the gait sequence to be analysed and to place the box constantly on the same location on the image, which will correspond to the same anatomical site.

The process of "bedding in" observed in the simulated walking test and in the test of insole reliability, dictated the recommendation for asking the patient to walk on the insole before the calibration. The necessity for a "bedding-in" process in the insole resulted also from the laboratory tests of cyclical loading **(Pitei et al., 1995)**, which showed that the insole should be conditioned by at least 60 seconds (and for further 60 seconds if using a new insole) of loading prior to calibration and that a trial walk be undertaken within a few seconds thereafter. This procedure aims to reach the plateau of the recoverable creep and allows the recordings to be made in the this part of the creep curve, which was shown to have a variability in the range of 3-4% **(Pitei et al., 1995; McPoil et al., 1995)**.

The pre-conditioning of the insole was also considered to overcome the initial creep. In the manufacturer's literature, Tekscan undertake 100% acceptance testing of insole on their bladder device, with two cycles up to 700kPa checking for track loss. Hence the insoles have already undergone two cycles at a high pressure, increasing the number of cycles would have an effect on the long-term irrecoverable creep behaviour, but there would not have a pre-conditioning effect on the recoverable dynamic creep. Also pre-conditioning of the insole before each trial in a bench top device might account for the long-term creep or separation, but it can not account for the temperature sensitivity or the recoverable creep. Therefore the F-Scan transducer was not pre-calibrated in a jig because of the drift in the sensitivity; nevertheless the manufacturer's recommendations for calibration were followed with due regard to the creep-like effect.

Therefore the initial walk before calibration serves several purposes such as reaching a plateau of the original non-recoverable creep, allowing the insole to conform to the curved shapes of the foot and temperature equilibration inside the shoe. This comes in agreement with another study recommending to place the insole inside the shoe for up to 5 minutes prior to calibration to allow the sensors to be loaded repeatedly and the temperature to stabilise to the environment of the shoe **(Koch, 1993)**. Lord and Hossein' study **(1994)** also supports our recommendations showing that temperature stability was gained over 3 minutes of use of the insole. The temperature sensitivity of the insole reported by the manufacturer was1.8 % for 1°C and in our study we found 1.1°C temperature change during a three run trial in a control subject, which is unlikely to influence significantly the level of recorded pressure. However the diabetic neuropathic patients with high foot pressures and a history of ulceration are characterised by higher skin temperature due to the presence of arterio-venous shunts in

their foot **(Edmonds et al., 1986),** but reduced vasodilatatory reactivity **(Newrick et al., 1988)** which would decrease the variations in their skin temperature. Therefore this may help avoiding variability of the insole due to changes in temperature. Also the neuropathic patients have dry skin and reduced sweating due to a concomitant sympathetic deficit, which would help avoid the effect of excessive moisture inside the shoe, which can infiltrate the margins of the insole giving false, although localised, high readings.

The calibration procedure against body weight would also take account of hysteresis and initial variability in insole manufacture, the temperature at which equilibration is gained, the long-term creep and the long-term degradation allegedly due to shear. However certain sources of error ought to be considered such as the hysteresis or different cells being pre-conditioned to different load levels, therefore increasing inter-cell variability. As regards hysteresis of the insole, reported by manufacturers to be typically in a range of 10-15%, ideally the body weight would be always loaded in the same direction for calibration. This was a reason for recommending the use of an insole per foot per patient, which would allow to place the insole always in the same position in the shoe, although the manufacturers describe that both sides of the insole as equally sensitive. As regards inter-cell variability, manufacturers have reported the individual cell variation being as much as 15% from the average and the amount of these single cells that could be seen across the 966 cell-sensor is estimated at 5. In order to overcome the problem of inter-cell variability it is recommended to calibrate over a large area to get the best average. This is attempted by asking the patient to load all the body weight on one foot, whilst it is checked concomitantly on the screen that the pressure is evenly distributed and then the 'Calibration' function is triggered.

Once the system is calibrated, it is advisable to start the first run immediately in order to take account for the recoverable (dynamic) creep seen in the laboratory experiments. However it is recommended not to record the first run, but to employ it as a learning curve run which would allow the patient to get used to the recording conditions as well. During this initial run it is also aimed to reach a suitable level of accommodation of the insole with the foot inside the shoe and to complete the "bedding-in" process. However sensitivity will continue to change slowly over several minutes even after the initial rapid rise is finished because of a irrecoverable, permanent creep-like element of the response. This necessitates calibration at frequent intervals namely at the beginning and at the end of the F-Scan test, in order to check for any

major sensitivity artefacts such as temperature or shear sensitivity. Nevertheless these variables highlight the importance of limiting the number of runs per one F-Scan test, which also resulted from the insole reliability trial: no more than 3 consecutive runs are recommended per patient: the first run for equilibration of the insole and patient's learning curve and the following two to be recorded.

The change in sensitivity during one F-Scan test, found in the laboratory experiments and in the simulated walking trial was shown to partially recover during the rest period. A minimum of 15 minutes break, which is feasible in clinical conditions, between tests using the same insole was found to be necessary for a suitable recovery of insole sensitivity.

The test of creasing and drop-out of the insole during un-consecutive runs highlighted another limitation of the insole regarding the total number of runs which one insole could undertake before an irrecoverable loss of sensitivity occurs. The mean life-time of an insole was shown to be of approximately 20-25 runs. Although for longitudinal studies one insole per patient would be recommended, the insensitive and often deformed diabetic foot could increase the wear-off factor by increasing the degree of manipulation and creasing, hence reducing the life-time of the insole. Mylar film is practically inextensible, so that local dynamic cross-talk effects are minimal. However, the long term effects of shear are to cause separation of the two layers of mylar from the ink layer. As this happens, the insole suffers a gradual degradation in sensitivity over a period. This would be a limiting factor on the life of the insole. This may support the findings of Rose et al. **(1992)** showing that the pressures measured decreased by the 20.5% at the twelfth trial and Birke et al. **(Birke et al., 1994)** reported an apparent 7% reduction in pressure after seven trials of walking 20 feet.

From the tests of run-to-run variability and inter-step variability, it was clear that there was not a significant difference between the pressures measured in different runs or in different steps of each run, in both the control group and the in neuropathic group. Therefore any step of any run could be used for analysis. In order to standardise the procedure, the second step of the second run or the mean of all steps are recommended to be considered. This suggestion is in agreement with the findings of Rose et al. showing that that F-Scan measurements were remarkably similar (mean 810, SD=20kPa) between subsequent steps within a trial **(Rose et al., 1992)**. Mueller et al. have also shown that acceptable reliability can be obtained on a single day of testing with as few as three steps, using the calibration suggested by manufacturer **(Mueller et**

al., 1996). Other studies also have suggested using a mean of three trials when using pressure measures from the EMED system **(Hughes et al., 1991)** and the Pedobarograph **(Holmes et al., 1991)**.

When measuring the foot pressures at different sites under the plantar surface in the control group and in the neuropathic group, higher pressures under the medial side of the forefoot and under the hallux were found in the neuropathic group, which seem to be characteristic for neuropathic patients even in early stages of neuropathy **(Boulton et al., 1987)** and are associated with an increased risk of foot ulceration **(Veves et al., 1992)**. Similar studies of foot pressures have shown also that most of the lesions of the neuropathic foot are secondary to excessive pressures on the forefoot **(Mueller et al., 1994;Cavanagh et al., 1992)**. Also from the study of the coefficients of variation, a larger variation in plantar pressures was demonstrated in neuropathic patients during continuous walking: 18.9% versus 10.3%, which was the highest coefficient of variation found in controls. In controls the variability of measurements on different days was found by others **(Rose et al., 1992)** to be similar to that of the measurements done on the same day, although they do not give the coefficients of variations, but the standard deviations of the measurements:SD=28.0kPa on the same day, SD=41.3kPa on separate days. Koch **(1993)** reported a intraperson coefficient of variation <23%, which was reduced to 15% if the sensor was allowed to 'warm-up' in the shoe for 5-10 minutes prior to testing. Also in another study **(McPoil et al., 1995)** when compared to EMED insole, the F-Scan insole was found to have a good to fair level of reliability between different days of testing, different trials, different steps for the first peak of force during the contact phase of the stance, whereas the reliability was found to be poor for the propulsive phase of the stance. Unfortunately there is no description in their methodology about any procedure regarding the insoles customisation to the conditions inside the shoe. These findings suggest that the F-SCAN offers an acceptable reproducibility in assessing the foot pressures during gait if the insole is accommodated to the conditions inside the shoe.

However, the greater variability found in neuropathic patients requires caution in interpreting the data from isolated steps when studying neuropathic patients. Another group **(Zhu et al., 1993)** using a portable, insole data-acquisition system consisting of seven pressure sensors placed in each insole under the pressures under posterior and anterior heels, the metatarsal heads and hallux demonstrated similarly an increased variability of walking in the neuropathic group and higher plantar pressures under first

metatarsals and posterior and anterior heels in the neuropathic group compared with the control group. Cavanagh and his group have also shown that there is an increased variability of loading in the forefoot compared to the rear foot in neuropathic patients **(Cavanagh et al., 1994)**. Therefore all these findings support the theory of increased variability in diabetic neuropathic patients which might play a role in the aetiology of plantar ulceration.

The inter observer variability of only 1.4% is in agreement with another study where the observer was compared to the computer's ability to pick up areas of peak pressure. The study found minimal differences (1-2%) providing that a consistent area was used to determine pressure and there was a consistent placement of the box **(Mueller et al., 1996)**. This supports our recommended technique to keep the area of the window constant and to place the box constantly on the same location on the image, which would correspond to the same anatomical location.

To be useful for clinical or research purposes, an in-shoe pressure system must be capable of providing reliable measures over time. The F-Scan linearity is comparable with other methods of foot pressure measurement: such as, the EMED-E barefoot measurements (r=0.85) **(Birke et al., 1994)** or when compared to the force platform (r=0.96) **(Mueller et al., 1996)** and the pedobarograph which showed that the pressure pattern of the different anatomical points was identical in the two systems and the range of pressure was similar, with small intra-subject pressure variability **(Nikolopoulos, 1996).** The F-Scan reliability has been reported to be good **(Mueller et al., 1996; Mueller et al., 1994)** especially if a methodology to stabilise the insole inside the shoe is used, as proven in this chapter and by other studies **(Koch, 1993; Lord and Hosein 1994)**.

Conclusion

A method for measurement of in-shoe foot pressures which achieves acceptable reproducibility in the study of foot pressures has been established and presented in this chapter. Foot pressure measured by analysis of in-shoe dynamic peak pressure using the F-SCAN is now feasible and adequately reproducible and should enable further exploration of the causative factors of foot problems, notably those of diabetic ulceration, in realistic shod conditions. A future use of in-shoe foot pressure measurements resides in the assessment of efficacy **(Chantelau and Haage, 1994; Albert and Christensen, 1994)** and design of bespoke footwear for diabetic patients.

Chapter 4. FOOT PRESSURES ASSESSMENT IN NEURO-ISCHAEMIC DIABETIC PATIENTS VERSUS NEUROPATHIC PATIENTS

4.1 Introduction

The aetiology of foot ulceration is multifactorial **(Murray and Boulton, 1995)** involving a complex series of factors of which some of the most important are peripheral sensory neuropathy and peripheral vascular disease (PVD).

Lower extremity arterial disease has been shown to have a high incidence in the diabetic population with up to 50% increase in the number of absent pulses in both diabetic men and women **(Abbott et al., 1990)**. Furthermore PVD is an important factor implicated in the aetiology of foot ulceration leading to an increased risk of amputation **(Pecoraro et al., 1990).** However PVD is rarely on its own but more frequently there is a combination of PVD and neuropathy in the neuro-ischaemic foot **(Boulton, 1996)**.

4.1.1 Types of foot ulceration in diabetes

Although ulceration has been described in detail in Chapter 1, the main features of ischaemic and neuropathic ulceration are summarised below.

<u>Ischaemic foot ulceration</u>

Vascular disease is a significant factor in over 60% of diabetic foot ulcers **(Walters et al., 1992)** and the ischaemic foot ulcer leading initially to gangrene of the toes, puts at risk of amputation the entire foot or leg. Various factors lead to reduced blood flow in the ischaemic foot:

- Atherosclerosis obliterans with thrombus formation and stenosis of the artery, which requires urgent assessment of the site and size of stenosis by angiography and concomitant angioplasty if possible, or surgical tibial-peroneal by-pass. This is achieved by using the patient's own saphenous vein and by connecting the vessels above the knee to the pedal vessels which frequently are unaffected **(Allen et al., 1993)**. This would be followed-up regularly in the Diabetic Foot Clinic until complete healing and re-gain of the arterial function.

- infection leading to microthrombi formation which can close the digital arteries of the toes with resulting septic vasculitis and gangrene. This would be treated with intensive intravenous antibiotic therapy according to the organisms found in the wound and their sensitivity.

- rarely, microemboli from the ulcerated plaques in the proximal vessels can occasionally cause the 'blue' or 'purple' toe syndrome, characterised by sudden pain and discoloration of the toes with a sharp demarcation between the ischaemic area and the area with normal perfusion. If the skin and/or muscle small arteries are blocked by these microemboli, painful petechiae or muscle pain can occur. If these symptoms are bilateral, the origin of the emboli is in the aorta or higher; if they are unilateral, the origin is in the iliac artery or below. The treatment requires removal of the source of embolization by vascular surgery **(Levin, 1995)**.

Vascular assessment

Different techniques of diagnosis and assessment of peripheral vascular disease have been described in detail in the introductory Chapter 2. The methods routinely used in the Diabetic Foot Clinic at King's College hospital are described as follows:

- a trained technician assesses all patients with clinical peripheral vascular disease, using Doppler ultrasound to measure the ankle blood pressure, which also permits recognition of an altered wave-form such as damping of the pedal artery waveforms caused by arterial narrowing. In patients with absent pulses but high ankle pressures, transcutaneous oxygen tension measurements are done in the clinic and then the patient is referred for further investigation to the Vascular Laboratory at King's College Hospital, which assesses the waveform pattern. Furthermore the patients diagnosed with critical limb ischaemia will be referred for arteriography in order to detect the areas of arterial stenosis.

<u>Neuropathic foot ulceration</u>

Peripheral neuropathy is present in over 80% of diabetic patients with foot lesions **(Caputo et al., 1994)**. Neuropathic foot ulcers occur at areas of pressure, due to high plantar pressures found in neuropathic patients at risk of ulceration **(Veves et al.,**

1992) or to repetitive moderate stresses on an insensitive foot with diabetic neuropathy, limited joint mobility, deformity (**Fernando et al., 1991**).

When the foot is well perfused, the repetitive stress and increase in pressure stimulate callus build-up, which further increases local pressure acting as a foreign body (**Young et al., 1992**) leading to ulceration from pressure necrosis, usually under the metatarsal heads or hallux on the plantar surface of the foot (**Levin, 1995**). Most of the neuropathic ulcers develop under the plantar surface of the foot.

Neuro-ischaemic foot ulceration

When the perfusion of the foot is not satisfactory, the possible complication of vascular dysfunction is added to the sensory loss and increases the risk of foot ulcers in diabetic patients. (**Boulton, 1991**) with the occurrence of another type of lesion, the neuro-ischaemic ulcer.

Most of the foot ulcers are due to a combination of neuropathy and ischaemia (**Walters et al., 1992**). The neuro-ischaemic foot ulcer is the commonest manifestation of ischaemia in the diabetic neuropathic foot, often manifested as failure of lesions to heal or ulcer recurrence. Such non-healing ulcers may occur over not very high pressure points, such as the medial aspect of the first metatarsophalangeal joint, over a malleolus, or at sites of pressure between the toes. However the callus formation is less prominent. Furthermore the ulceration tends to occur less on the plantar surface, and more at sites of shear stress, as described previously (**Jeffcoate et al., 1993**) due to ill-fitting shoes and the resulting ischaemic pressure necrosis.

However the pressure loading in the shoes of patients with neuro-ischaemic ulcers has not been studied previously; neither regarding the shear, horizontal component of the forces acting on the foot, nor regarding the vertical forces developed inside the shoe.

The shear transducers still await modernisation, whereas the new methods for dynamic in-shoe foot pressure measurement such as F-Scan have been developed and allow assessment of the pressures developed at the shoe-foot interface. This would be predominantly the normal force although a small component of shear force can be detected at the margins of the insole.

4.2. Aims of the study

The aims of the present study were to apply the methodology established in the previous chapters for the use of F-Scan, in order to assess the pressures developed at the shoe-foot interface in diabetic neuro-ischaemic patients. In contrast to neuropathic patients who develop ulcers under the plantar surface of the foot, the diabetic patients with peripheral ischaemia (who also have a degree of neuropathy and impaired sensation) develop ulcers on the margins of the foot.

Neuropathic ulcers develop at sites of high pressure on the plantar surface **(Boulton et al., 1983)**. High plantar pressure seemed to be a multifactorial condition relating mostly to the limitation of joint mobility in the foot and to neurological dysfunction. Most of the current foot pressure studies (static or dynamic) have been performed barefoot **(Veves et al., 1992; Fernando et al., 1991)**, but it is also important to measure the peak plantar pressures within the shoe during normal walking conditions **(Cavanagh et al., 1985; Lord and Hosein, 1994)**. However plantar pressures have never been measured in neuro-ischaemic patients. The hypothesis could be that their plantar pressures are lower than in neuropaths.

Therefore the aims of our present study were to measure vertical in-shoe foot pressures during walking in neuro-ischaemic diabetic patients and to compare them to diabetic patients with neuropathy alone.

The study was divided in two parts:

- the first part aimed to measure the in-shoe plantar pressure distribution during walking in neuro-ischaemic diabetics and compare them to diabetic patients with neuropathy alone and also to two control groups, such as diabetic patients without neuropathy and non-diabetic subjects.

- the second part of the study aimed to analyse the way the pressure was loaded during walking in each group. Was the pattern of pressure loading consistent from step to step or was there variability between steps?

4.3 Patients and methods

4.3.1 Selection and characteristics of patients

Four groups of patients were selected to take part into the study:

Group A: 18 neuropathic patients with a previous history of foot ulceration, no history of intermittent claudication, foot pulses palpable bilaterally and a brachial-ankle pressure index equal or higher than 1. Neuropathy was defined by the absence of ankle reflexes accompanied by abnormal vibration perception threshold (VPT>20 Volts) measured with a Biothesiometer (Biomedical Instruments Co., Ohio, USA).

Group B: 14 neuro-ischaemic patients with a history of ulceration on the margins of the foot. Peripheral ischaemia was defined as a pressure index less than 0.8, absent foot pulses. They also had a degree of neuropathy as their mean VPT was 29.3±13.5 Volts, which was not significantly different from the mean VPT of the neuropathic patients. None of the neuro-ischaemic patients complained of ischaemic pain.

Group C: 11 diabetic controls without complications. All of them had present ankle reflexes and bilateral foot pules palpable. The mean VPT was 9.9±2.7Volts and their pressure index was equal or higher than 1.

Group D: 15 non-diabetic controls of whom none had a family history of diabetes.

Table 4.1 Clinical details of patients

	No.	Age (years)	Diabetes duration (years)	Diabetes type 1/2	VPT (V)
Controls	15	49.6±11.9	-	-	7.0+ 0.5
Diabetic Controls	10	57.6±10.8	9.2±9.7	4 / 6	9.9± 2.7
Neuropathic patients	18	55.4±16.0	21.5±12.7	8 / 10	38.7±12.7
Neuro-ischaemic	14	63.5± 9.8	17.4±14.4	6 / 8	29.3±13.5

The VPT was not statistically significant (NS) different between control subjects versus diabetic control patients and between neuropathic versus neuro-ischaemic patients.

4.3.2 Methodology

Foot pressures measurement was performed as recommended in the previous chapter.

Recording

The patient was asked to walk at his own normal pace, on a flat surface. The recording of foot pressures was done concomitantly for 4 seconds. All the recordings were done in the same direction of walking. The recording of foot pressures was performed in standard shoes (Clarks 'Swing Low' trainers) which were used because of the reported variation with different types of footwear. The patients were given standard pop socks because hosiery can also alter the foot pressures (**Veves et al., 1989**).

Analysis of pressure recording

F-SCAN data recording from different runs were recalled and analysed in two active windows on the screen. The gait mode displayed a two-dimensional representation of the plantar pressures sequentially from heel-strike to toe-off. The increase in pressure was seen as a change in colour of the pressure map from blue to red as a function of time. The "Average" function from the screen was activated, in order to allow a smoothing effect on the immediate surrounding cells and to reduce the possibility of artefacts.

In order to determine the distribution of pressures under the foot and detect if there is any tendency towards a pattern of pressure distribution in different groups of patients, the analysis investigated four areas of interest under the four main areas of the foot: the big toe, the medial and lateral side of the forefoot and the heel. The size of the box was adjusted accordingly with the area of interest: (15mm*15mm) for the big toe and an area of (45mm*45mm) for the medial or lateral forefoot and heel.

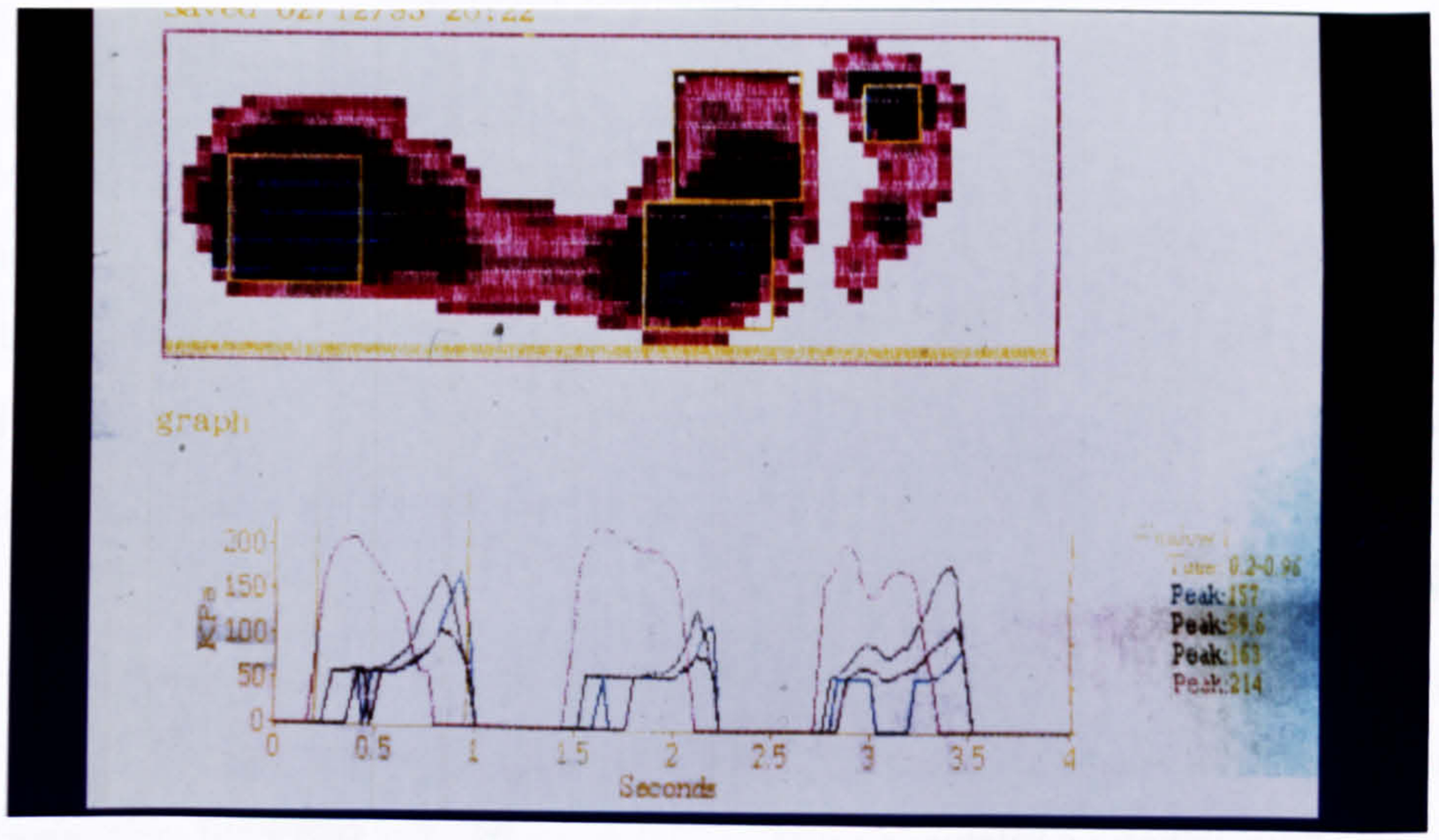


Fig. 4.0 Peak plantar pressures analysed under the four main areas of the foot on a F-Scan recording

The *peak plantar pressures* were obtained from the pressure-time graphs for the areas of interest by moving the cursor along until the peak of each graph representing the pressures developed under a specific area during each step, was reached. A mean of all pressures measured in each step of each run was calculated for a patient.

The *highest peak plantar pressure* in a patient was calculated as the greatest pressure value observed under a specific area during all steps of all runs.

As a new version of F-Scan software (3.8) was received recently (1996), the recordings were re-analysed regarding the *maximum plantar pressure* developed by a patient during a gait stance. A standard box (10*10mm) was applied automatically by the programme on the area of highest pressure detected by the computer under the foot.

Analysis of pattern of pressure

In order to investigate if the pressures were loaded on the plantar surface consistently in every step of every run, their interactions in different steps of different runs were analysed in all groups of patients to describe the pattern of pressure loading.

The interactions between the first and second step in the first and second runs were calculated in order to find out if the pressures of the first step in the first and second runs were loaded in a similar way to the second step in the first and second runs, referred to subsequently as the interaction for run by step.

4.3.3 Statistical analysis

Data are presented as Mean ± SEM. Data were tested for normality and then were analysed using the parametric Student's t-test to compare pressures measured in similar anatomical locations in the four groups of subjects: neuro-ischaemic patients versus neuropathic patients versus the two groups of control subjects. The plantar pressures were measured under the big toe, under the medial and lateral side of the forefoot and under the heel.

The pattern of pressure loading was analysed as the interaction for run by step in the four groups of subjects:

- non-diabetic controls
- diabetic control patients
- neuropathic diabetic patients
- neuro-ischaemic diabetic patients.

The one-way analysis of variance for measured pressures was used considering the run and the step as main effects and their interactions were calculated in the pattern of pressure analysis.

4.4 Results

4.1.1 Mean peak plantar pressures in the four groups of subjects

The diabetic controls manifested a slight trend to higher peak pressures than non-diabetic controls, although this was not statistically significant, except under the hallux (Table 4.2).

The neuropathic patients showed significantly increased plantar pressures when compared to both control groups under the lateral and medial sides of the forefoot, although the diabetic controls had pressures under the hallux and the heel which were not statistically different from the neuropathic patients. However the neuro-ischaemic patients showed significantly greater pressures than all the other three groups (Fig. 4.1)

Table 4.2 Mean peak plantar pressures (kPa) measured under hallux, lateral and medial forefoot and heel in the 4 groups of subjects

Patients	Hallux	Lateral forefoot	Medial forefoot	Heel
Controls (C)	115.0±12.8	127.3±17.8	151.7±19.6	134.4±15.7
Diabetic Controls (DbC)	170.0±22.8	138.9±15.9	139.0±20.5	148.9±22.3
Neuropathic patients (Np)	171.2±16.5	182.0±16.2	211.8±20.1	217.3±24.9
Neuro-ischaemic patients (Neuro-Isch)	272.5±35.7	263.9±30.5	267.1±34.5	245.8±32.3
Comparisons between groups				
C vs DbC	p=0.04	p=0.63	p=0.66	p=0.60
Np vs C	p=0.02	p=0.03	p=0.05	p=0.02
Np vs DbC	p=0.96	p=0.017	p=0.02	p=0.07
Neuro-Isch vs C	p=0.001	p=0.001	p=0.008	p=0.005
Neuro-Isch vs DbC	p=0.02	p=0.001	p=0.004	p=0.02
Neuro-Isch vs Np	p=0.007	p=0.01	p=0.15	p=0.49

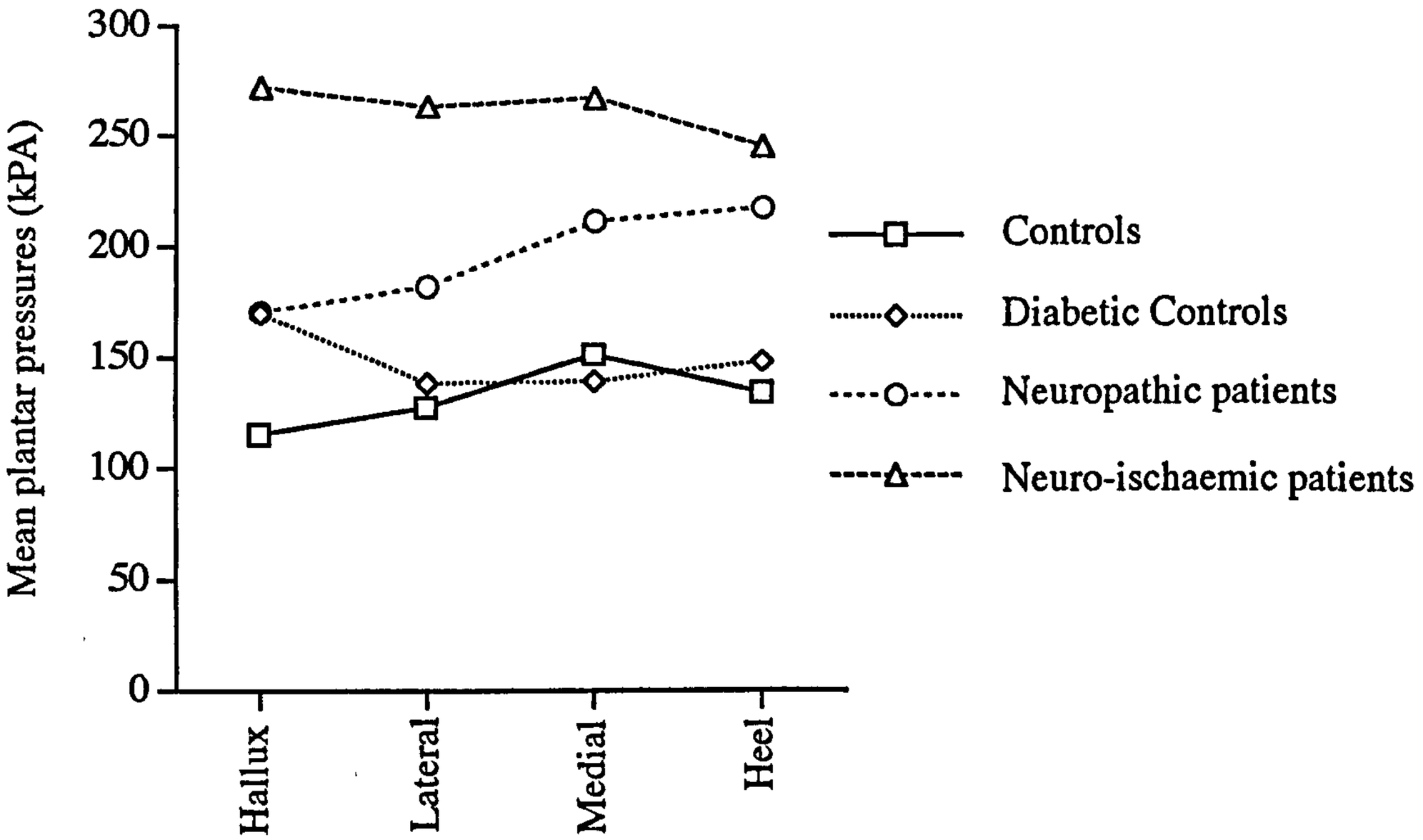


Fig. 4.1 Graphic comparison of the mean peak plantar pressures measured in the four groups: non-diabetic and diabetic controls, neuropathic and neuro-ischaemic patients

Table 4.3 Highest peak plantar pressures (kPa) measured under hallux, lateral and medial forefoot and heel in the 4 groups of subjects

Patients	Hallux	Lateral forefoot	Medial forefoot	Heel
Controls (C)	162.5±28.4	156.0±22.1	204.6±37.8	188.2±33.0
Diabetic Controls (DbC)	190.8±28.1	158.9±17.5	167.0±26.4	166.1±22.8
Neuropathic patients (Np)	195.3±19.3	212.0±19.2	242.0±25.1	240.1±28.1
Neuro-ischaemic patients (Neuro-Isch)	344.0±49.2	331.6±45.7	349.1±49.5	301.0±39.1
Comparisons between groups				
C vs DbC	p=0.48	p=0.92	p=0.43	p=0.59
Np vs C	p=0.32	p=0.06	p=0.03	p=0.24
Np vs DbC	p=0.89	p=0.06	p=0.06	p=0.07
Neuro-Isch vs C	p=0.01	p=0.002	p=0.02	p=0.03
Neuro-Isch vs DbC	p=0.01	p=0.002	p=0.004	p=0.007
Neuro-Isch vs Np	p=0.003	p=0.01	p=0.04	p=0.21

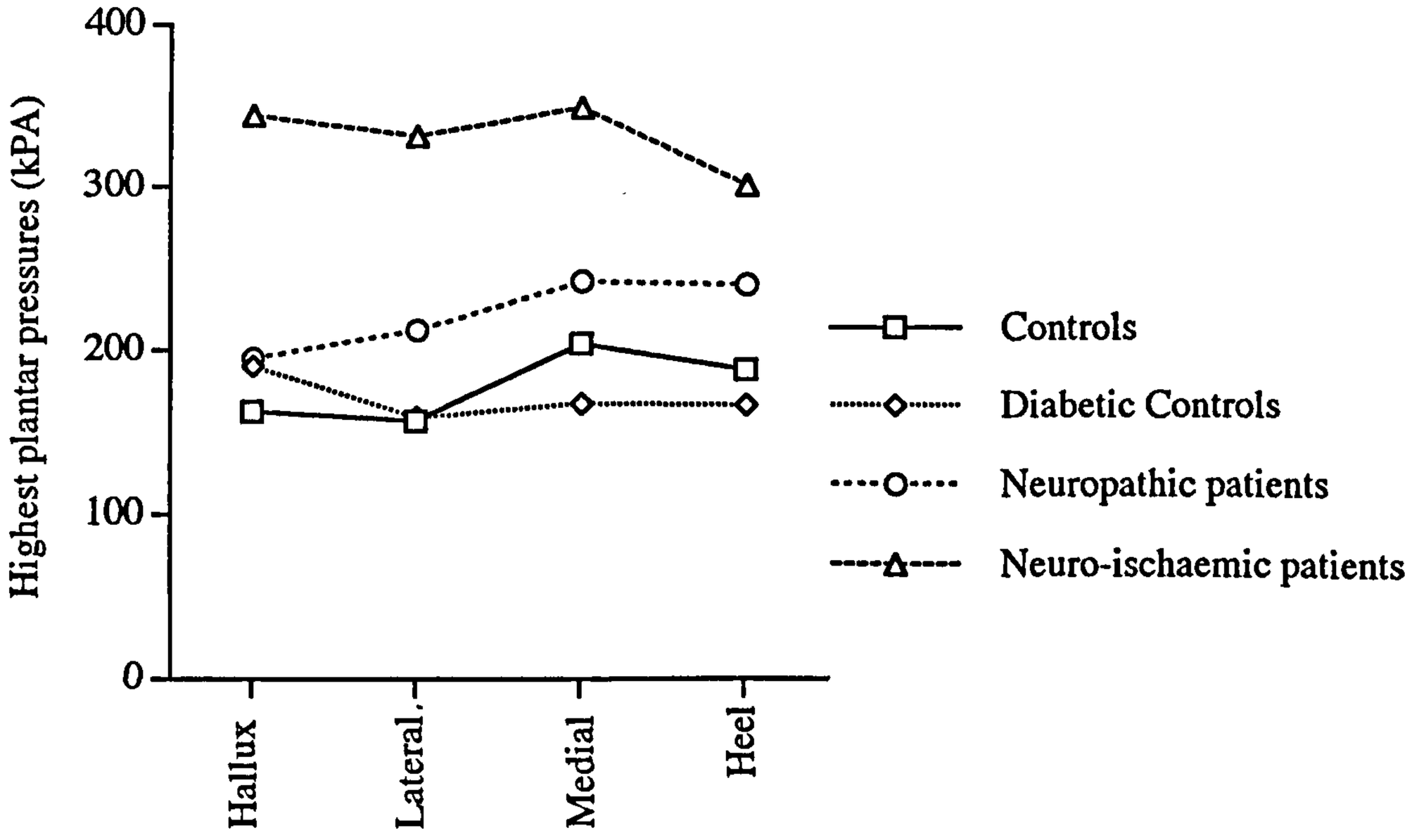


Fig. 4.2 Graphic comparison of the highest peak plantar pressures measured in the four groups: non-diabetic and diabetic controls, neuropathic and neuro-ischaemic patients

Table 4.4 Maximum peak plantar pressures (kPa) and their location in the four groups of subjects

Patients	Maximum pressure (kPa)	Number of subjects which had their maximum pressure located under					
		Hallux	1st MTH	2nd MTH	3rd MTH	4th MTH	5th MTH
Controls (C)	365.1±49.8	2	4	6	3	0	0
Diabetic Controls (DbC)	310.2±34.7	5	2	3	1	0	0
Neuropathic patients (Np)	482.8±68.6	6	6	3	2	0	1
Neuro-ischaemic patients (Neuro-Isch)	757.6±135.9	5	2	2	1	4	0

Comparisons between groups	
C vs DbC	p=0.3,NS
Np vs C	p=0.04
Np vs DbC	p=0.03
Neuro-Isch vs C	p=0.007
Neuro-Isch vs DbC	p=0.008
Neuro-Isch vs Np	p=0.04

MTH= metatarsal head

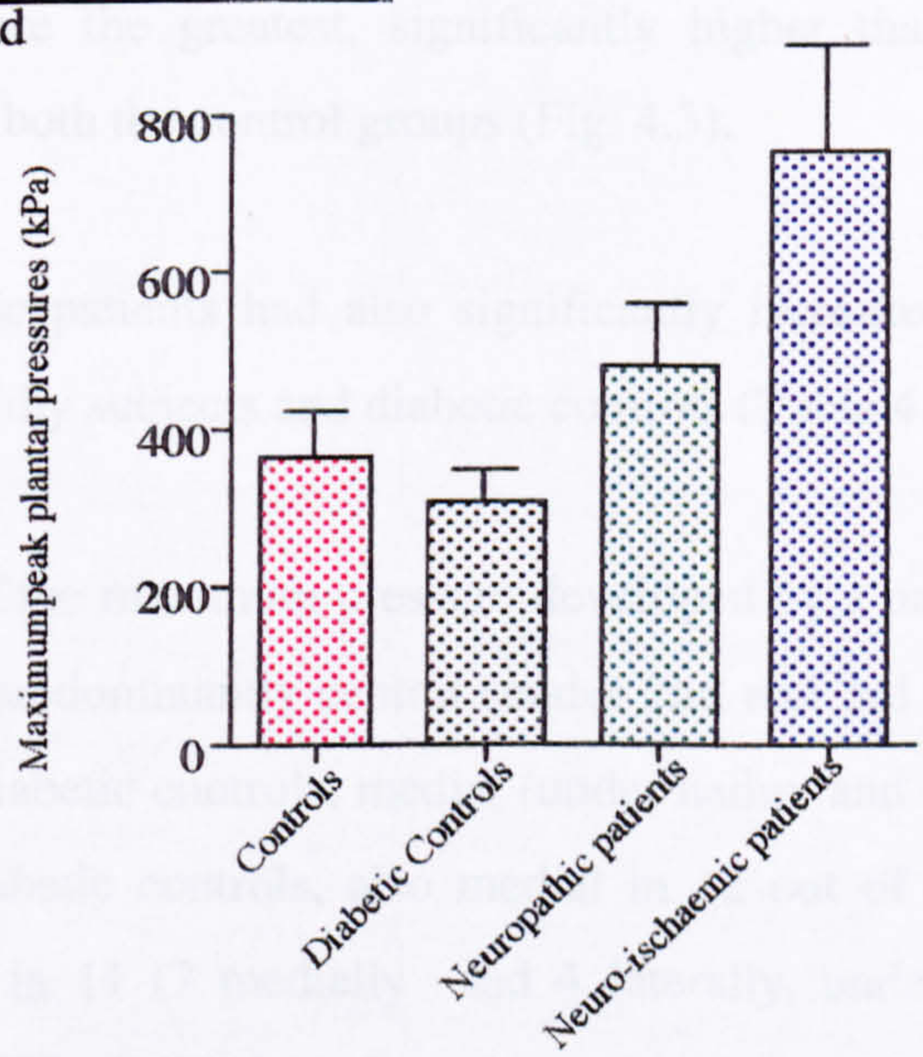


Fig. 4.3 Graphic comparison of the maximum plantar pressures measured in the 4 groups: non-diabetic and diabetic controls, neuropathic and neuro-ischaemic patients

4.4.2 Highest peak plantar pressures in the four groups of subjects

Again the highest peak plantar pressures in each area of the foot were significantly elevated in the neuro-ischaemic group when compared to the other 3 groups (Fig. 4.2).

In the neuropathic patients a trend was found towards greater pressures than in the control groups. However this was not statistically significant, except for the medial side of the forefoot.

The highest measured pressures in the control subjects did not differ from the pressures measured in the diabetic control patients (Table 4.3).

4.4.3 Maximum plantar pressures in the four groups of subjects

The maximum pressures developed under the plantar surface by the neuro-ischaemic patients were the greatest, significantly higher than those found in the neuropathic group and both the control groups (Fig. 4.3).

The neuropathic patients had also significantly increased maximum pressures when compared to healthy subjects and diabetic controls (Table 4.4).

The location of the maximum pressure developed by a patient under the plantar area was found to be predominantly central (under 2nd and 3rd metatarsal heads) in 9 out of 15 (60%) non-diabetic controls, medial (under hallux and 1st metatarsal head) in 7 out of 11 (63%) diabetic controls, also medial in 12 out of 18 (66%) neuropathic patients and marginal in 11 (7 medially and 4 laterally, under the 4-5th metatarsal heads) out of 14 (78.5%) neuro-ischaemic patients.

4.4.4 Pattern of pressure loading in the two control groups of diabetic and non-diabetic subjects

The pattern of pressure loading in diabetic and non-diabetic control subjects was consistent: in both groups the pressures behaved in a similar way between steps from the first to the second run. The pressures decreased from first run to the second run for both first and second steps (Fig. 4. 4). There was not a statistically significant difference between the interactions for run by step in either the non-diabetic control group ($p<0.79$) and neither in the diabetic control group ($p<0.56$).

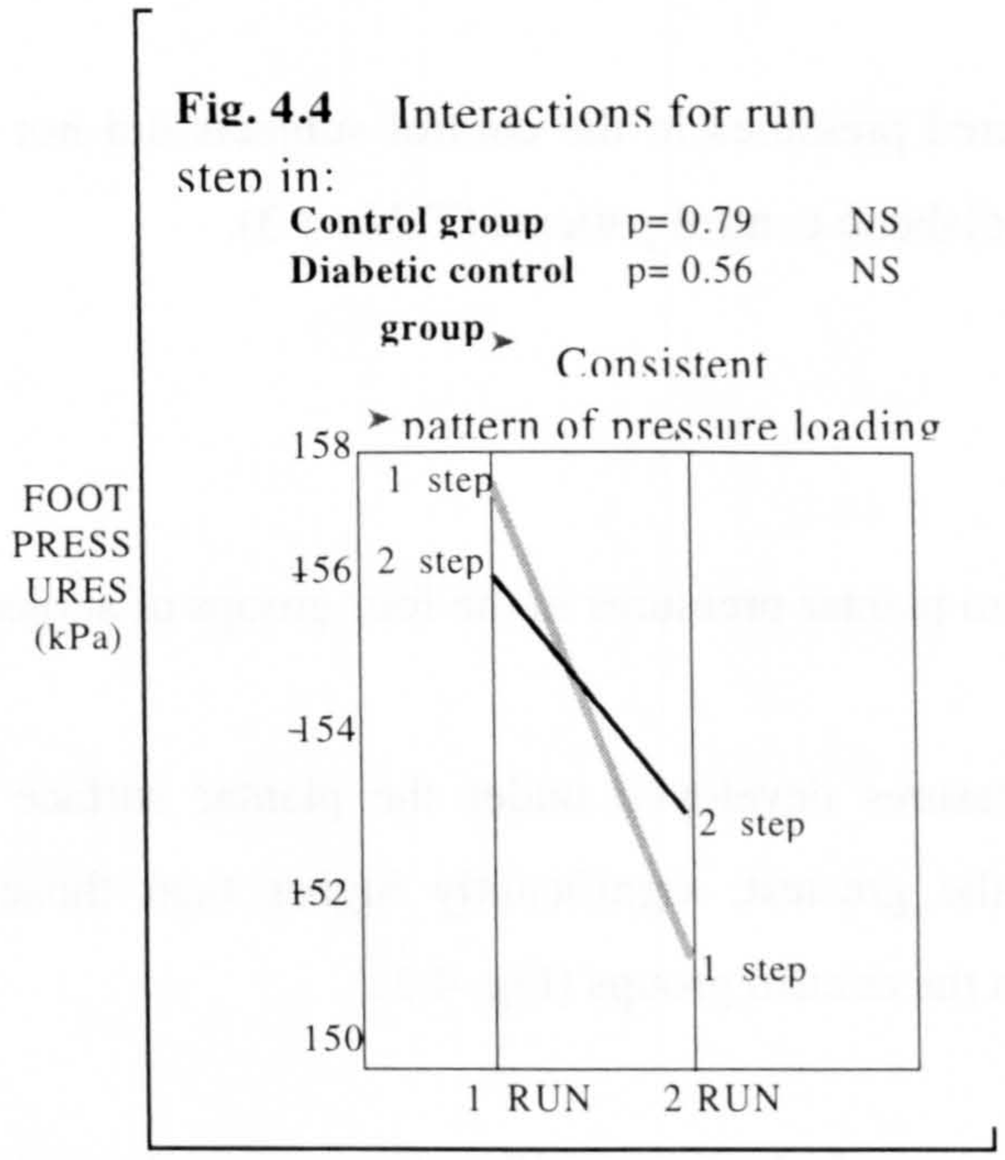


Fig. 4.4 Interactions for run step in:

4.4.5 Pattern of pressure loading in neuropathic diabetic patients

In the group of diabetic neuropathic patients the pattern of pressure loading was found to be inconsistent. The pressures decreased from the first run to the second run for only the first step, whereas the second step showed an increase pressure from the first run to the second run (Fig. 4. 5). Although the actual variation in pressure was minimal and not statistical significant, what was found to be statistically significantly different was the interaction between the two trends ($p<0.05$) suggesting that the pressures were loaded in an inconsistent manner between steps and runs.

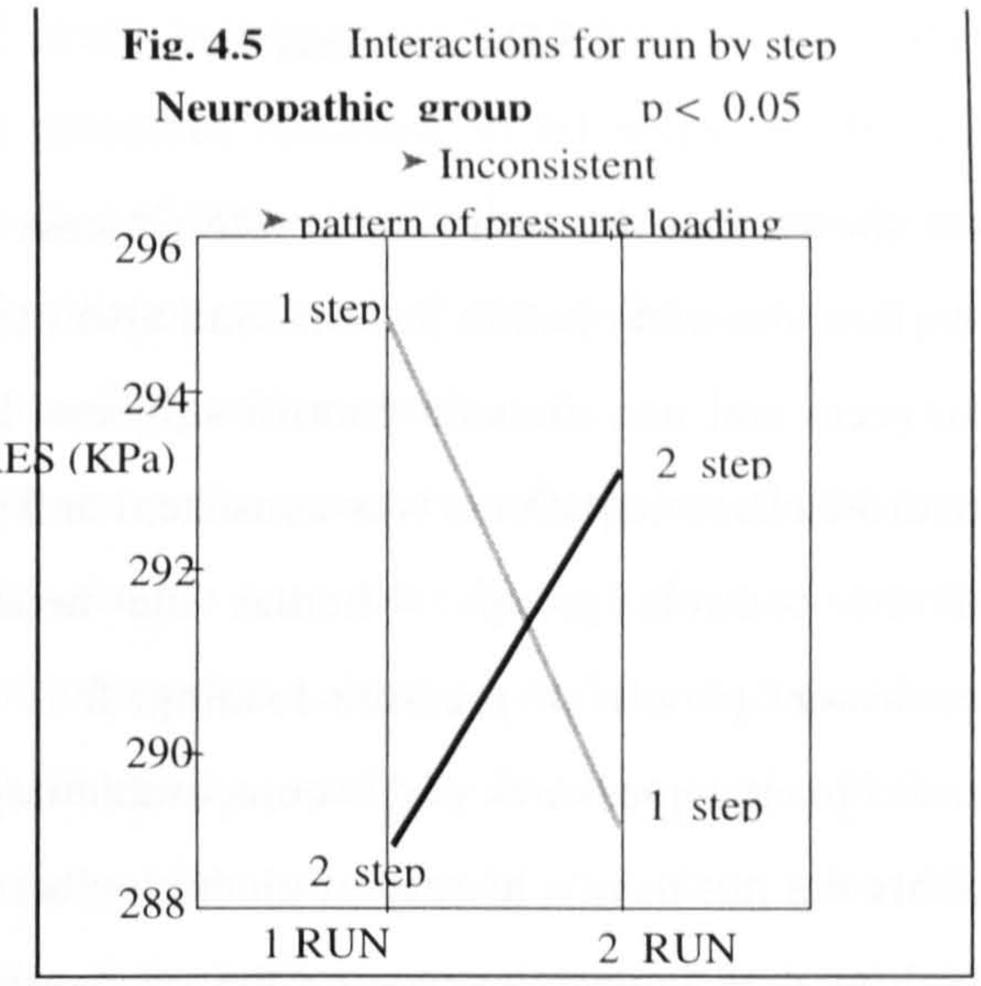


Fig. 4.5 Interactions for run by step

Neuropathic group $p < 0.05$

4.4.6 Pattern of pressure loading in neuro-ischaemic diabetic patients

However the neuro-ischaemic group presented a similar consistent pattern of pressure loading to the control groups: the interaction for run by step was found to be not statistically different ($p=0.19$). The pressures decreased between the first and second runs for both steps (Fig. 4. 6).

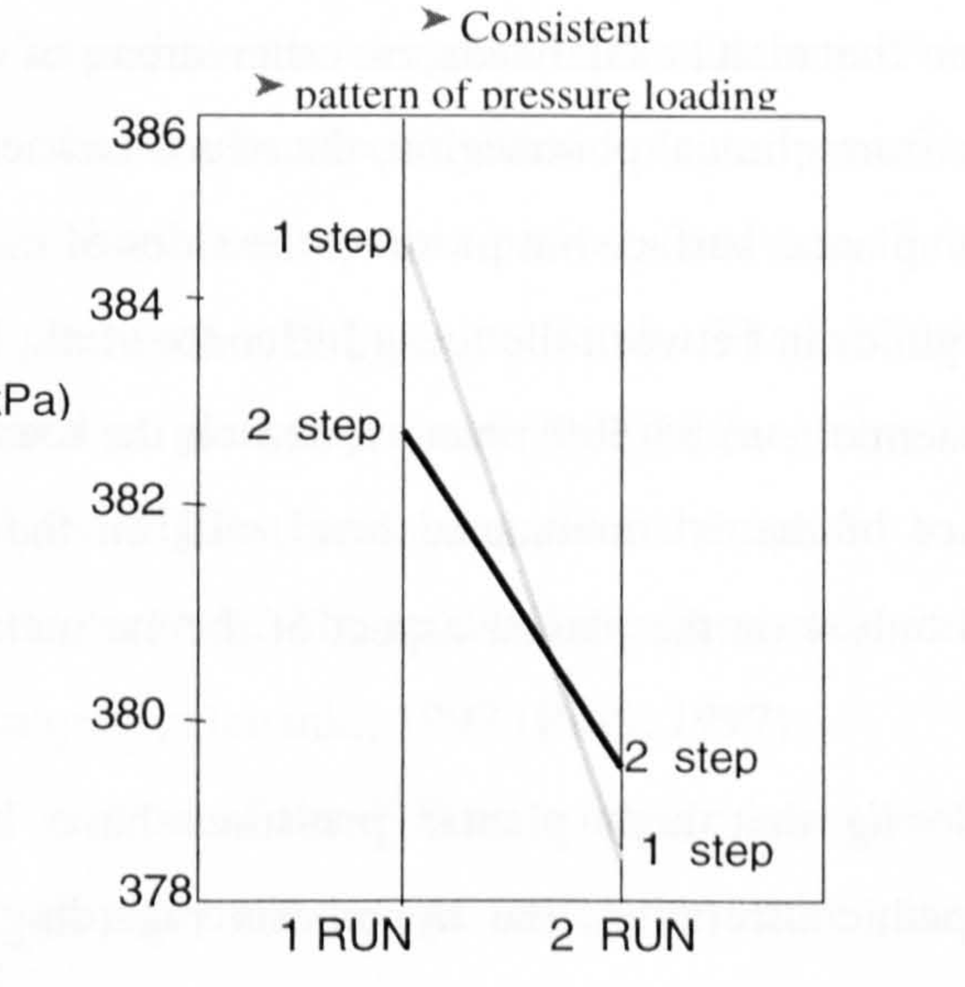


Fig. 4.6 Interactions for run by step in:

Neuro-ischaemic group $p = 0.19$, NS

4.5 Discussions

This study has shown that the neuro-ischaemic patients had the highest plantar pressures, higher even than the neuropathic patients and also increased when compared to diabetic control subjects and non-diabetic control subjects. However the pattern of pressure loading in neuro-ischaemic patients was consistent and similar to the pattern of pressure loading of the controls groups, whereas the neuropathic patients have demonstrated an inconsistent pattern of pressure loading. It is interesting to note that despite having increased plantar pressures and a comparable degree of neuropathy, the neuro-ischaemic patients did not have a history of ulceration on the plantar surface. We believe these observations may have relevance to the mechanism of ulceration in the neuro-ischaemic and neuropathic foot.

Neuropathic ulceration has been studied extensively and its multifactorial aetiology has been detected (**Boulton AJ, 1994**). The measurement of foot pressures was considered to be essential when characterising the risk of neuropathic ulceration considering their important role in its pathogenesis. However there were no similar studies assessing the foot pressures in the neuro-ischaemic diabetic patient. These patients have also a high risk of ulceration, firstly, because of their peripheral vascular disease and secondly, because most of them have an underlying degree of neuropathy.

The majority of neuropathic foot ulcers develop under the plantar surface, predominantly under the metatarsal heads or other areas of high pressure, such as deformity. However from clinical observation, the neuro-ischaemic patients tend not to develop ulcers on the plantar surface but more on the sides of the foot (**Edmonds, 1987**) or on the upper margin or in between the toes (**Jeffcoate et al., 1993**). In a study of 148 ulcers in neuro-ischaemic feet, 88(59%) were found on the toes, 7 were interdigital, 14 on the lateral surface of the 5th metatarsal head, 12 on the medial side of the 1st metatarsal head and only 4 on the plantar aspect of the 1st metatarsal head (**Edmonds, 1987**).

Also considering that high plantar pressures have been implicated in the aetiology of neuropathic ulceration, the hypothesis regarding the foot ulceration in neuro-ischaemic patients was that they would have lower vertical pressures, as they tend not to develop ulcers underneath the foot. This hypothesis was not confirmed by the present findings, which actually has shown that the mean plantar pressures under all

areas of interest on the plantar surface: the hallux, the medial and lateral sides of the forefoot and the heel were higher even than those in the neuropathic patients. By meaning all the peak pressures recorded in all steps of all runs in each patient we attempted to obtain a value of pressure which represents the overall, constant loading on the foot as a method for the assessment of one of the causative pathways in neuropathic ulceration, the constant and repetitive stress.

However by meaning the pressure values, we might have missed the highest peaks of pressure, which are the ones more likely to lead to ulceration in the neuropathic foot with a history of ulceration, characterised by increased plantar peak pressures (**Boulton et al., 1984**). In another study by Boulton et al.. all the feet with a history of ulceration had abnormally high pressures at the ulcer sites (**Boulton et al., 1983**). Therefore we also analysed the highest peak pressures under the four areas of interest in the four groups. Again the highest peak plantar pressures were present under the neuro-ischaemic foot, whereas the neuropathic patients had lower pressures than the neuro-ischaemic patients did, but higher than both control groups. The highest plantar pressures developed by the neuropathic patients were significantly increased only under the medial side of the forefoot, which has been recognised as the area most prone to ulceration in neuropathic patients (**Boulton et al., 1983**). The pressures measured under the other areas of the foot showed a trend to increase without statistical significance. Nevertheless they could be clinically significant if applied repetitively on an insensitive foot.

Another similar experiment in progress in the Diabetic Foot Clinic has used the Musgrave platform to assess the barefoot dynamic plantar pressures in diabetic patients with ischaemia versus diabetic neuropathic patients and non-diabetic controls using a protocol similar to the one used in the present study. The preliminary results obtained with this different method of plantar pressure assessment, have shown that the neuro-ischaemic patients had the highest pressures when compared to neuropathic diabetic patients and non-diabetic controls. The results have been presented at the International Diabetes Federation Congress, Helsinki, 1997 (**Pitei, 1997**).

Recently a new version of the F-Scan software has allowed the assessment of maximum pressure developed by a patient under the entire plantar area and the site where this is located. Therefore on re-analysis of the data obtained in all patients, it was found that the neuro-ischaemic patients had developed indeed the highest maximum pressures, significantly higher than all the other groups, but not statistically different

from the neuropathic group who also developed increased maximum plantar pressures. Furthermore when analysing the location of the maximum pressure, 78.5% of neuro-ischaemic patients developed the maximum plantar pressures towards the margins of the foot, whereas 66% of neuropathic patients loaded their maximum pressures under the medial side of the forefoot. These results supported the clinical observations regarding the areas where foot ulceration tends to occur in neuropathic or neuro-ischaemic patients. Likewise these findings would suggest that the maximum plantar pressure measurements could be a useful parameter in detecting the location of high plantar pressures in patients at risk of foot ulceration.

Another significant parameter regarding characterisation of pressure distribution during gait has been highlighted in recent literature, namely the pressure-time integral (**Shaw, 1995**). The total stress depends on the amplitude of pressure inside the shoe and the length of time the pressure was applied for. Therefore it is not only important to know how high the pressures inside the shoe are, but also for how long have they have been loaded. It must be said that in this study the pressure-time integrals were not measured, because the F-Scan methodology was not set up to do so initially, and the primary question of the study concerned purely the amplitude of plantar pressures developed inside the shoes of the four groups of patients. Also the facility to measure pressure-time integrals was not available to us from the manufacturer until a late version of F-Scan software, which was not totally validated by the time this thesis has been written. However further studies assessing the pressure-time integrals and the time characterisation of the foot pressures in the neuropathic and neuro-ischaemic patients versus the control subjects and diabetic controls are needed.

Thus, although the neuro-ischaemic patients did not develop ulcers under the plantar surface their vertical plantar pressures were consistently high, and even higher than the neuropathic patients who tend to develop ulcers underneath the foot. It must be noted that the neuro-ischaemic patients had also a degree of neuropathy, which was not significantly different from that of the neuropathic patients. The degree of neuropathy was above the vibration perception threshold considered to be of risk for ulceration, as described by Young et al.. (**Young et al., 1994**). Therefore some increase in the plantar pressure could have been expected considering that these neuro-ischaemic patients did have a degree of neuropathy. However if their pressures were higher than those of the neuropathic patients, why did they not develop ulcers underneath the foot?

A possible explanation may be regarding the level of activity. This aetio-pathological factor implicated in the ulcer formation was considered to be essential by Cavanagh et al. (**1994**). As an added factor to the level of activity, the type of activity is also important when assessing the foot pressures as the amount and the type of activities during daily living may affect the foot (**Rozema et al., 1996**). It is important to know how often and for how long an area on the plantar surface is subjected to a repetitive and high stress. In our study, it is possible that the neuropathic patients simply continued to walk on areas of quite high pressure, whereas the neuro-ischaemic patients simply walked less because of possible intermittent claudication and general frailty, which prevents them from actively walking on these areas of high pressure.

The neuropathic foot, in response to continuous repetitive stress and high pressures, develops 'hot' spots and callus build-up (**Levin, 1995**) which itself has been implicated in the aetiology of ulcer formation, acting as a foreign body and increasing further the pressures (**Young et al., 1992**). In contrast, the neuro-ischaemic foot, which is defined by both ischaemia and a degree of neuropathy, tends not to build-up so much callus, possibly because of the poor blood supply. This is in contrast to the neuropathic foot which in the presence of a good blood supply develops callus at the sites of high pressures and this has been proven to be a forerunner of ulceration on the plantar surface (**Edmonds, 1987**). The findings of high pressure in neuro-ischaemic patients seem not to be related to the callus formation.

Furthermore in the neuro-ischaemic foot there is possibly reduced subcutaneous tissue due to poor blood supply. This may reduce the cushioning effect of the soft tissue and may account for the high pressures found in these patients. Likewise, it may be that the properties of the soft tissue in neuro-ischaemic patients are altered in comparison to the pure neuropaths who have a good blood supply with palpable pulses. It might not only be that the soft tissue is thinner but its intrinsic compressibility, and elasticity are altered as the tissue is suffering from 'malnutrition' because of the continuos ischaemic process. Observations on amputated neuro-ischaemic legs indicate that their muscles can be atrophic (Personal communication. **Edmonds, 1996**). The properties of the soft tissue have just recently been considered as important in the aetiology of ulceration. The thickness of the soft tissue and the alignment of bones were measured from standing weight bearing X-rays and they have been shown to be useful predictors of elevated plantar pressures under metatarsal heads in walking (**Cavanagh et al., 1994**).

Furthermore Brink has shown in ten neuropathic patients with a history of ulceration that soft tissue at the sites of previous ulceration over the metatarsal heads, was significantly harder than at other sites in the same feet or in the control feet, although the degree of limited joint mobility was similar in neuropathic patients to that in the older controls. He also found that the peak plantar pressures were significantly higher at this areas of induration of the plantar pad and concluded that the induration of the soft tissue may predispose to recurrent foot ulcers in diabetics by decreasing the shock absorption capacity of the plantar pad (**Brink, 1995**). Future studies are awaited to elucidate the role of soft tissue in the diabetic foot ulceration and specifically in the neuro-ischaemic foot.

An atrophic, thin skin on the foot may be more vulnerable to the shear forces developed on the margins of the foot. Ischaemia of the superficial layers of the dermis allows cleavage to occur in response to shear stresses with subsequent formation of blisters (**Goodfiled et al., 1986**). The shear forces developed at the shoe-foot interface have been implicated, although the exact mechanism still awaits elucidation - as discussed in the previous chapter, in the aetiology of foot ulceration in neuropathic patients with concomitant vascular disease. The neuro-ischaemic foot has a decrease in the blood flow with subsequent tissue ischaemia, which makes the soft tissues of the foot more sensitive to stresses developed inside the shoe from ill-fitting shoes, which would lead to localised areas of pressure due to the shear stresses (**Jeffcoate et al., 1983**). This might lead to the necrosis of the ischaemic tissue at the sites of friction with the tight shoes (**Edmonds, 1987**) before there is time for the high vertical pressures to act on the plantar surface and lead to ulceration, especially if the level of activity is reduced (**Cavanagh, 1995**).

In the absence of a clinically available shear transducer, attempts to determine a relationship between anterior-posterior shear and maximum plantar pressures were made in 30 subjects (**Cornwall et al., 1995**). The results of this study have shown that by complex analysis of a combination of peak force, time to peak pressure and stance duration time, the anterior-posterior shear can be predicted. However this theoretical attempt underlines once more the need for technologies to be developed and for further studies to measure the shear forces inside the shoe, with special interest in the neuro-ischaemic patients who possibly are the most vulnerable to shear stress.

Another possible explanation of the study findings may be that different groups of subjects may have different ways of loading the pressures on the plantar surface. Therefore an attempt was made to find a way to analyse the pattern of pressure loading in different steps of different runs by describing the interactions between the steps and runs of the patients in the four groups. Both the control groups: diabetic patients without neuropathy or ischaemia and non-diabetic control subjects, had a consistent pattern of loading. The neuro-ischaemic patients also showed a similar consistent way of loading the pressures on the plantar surface of the foot. These findings suggest of a repeatable, uniform gait. However the only group showing a significant interaction between the pressures developed in each step of each run, was the neuropathic group, which developed an inconsistent pattern of pressure loading: they increased or decreased the pressures of the first step from the first run to the second run, with a contrary tendency for the pressures of the second step. For example, if the pressures of the first step were increased in the second run, the pressures of the second step were decreased in the second run. Although the change in pressure actually was not statistically significant, what was significant was the interaction between the direction of change (increase/decrease) of the pressures developed in the steps of the first and second run.

Therefore, it seems that the neuropathic patients have a higher variability of gait and of pressure loading. This is in agreement with other findings reporting problems with gait and posture in neuropathic patients, who were 15 times more likely to report injuries, these results being strongly indicative of an effect of neuropathy on gait (**Cavanagh et al., 1992**). Furthermore increased unsteadiness, and uncertainty in neuropathic patients were reported as biomechanical consequences of diabetic neuropathy, which leads to loss of large fibre proprioception and somatic feedback from receptors in the feet (**Cavanagh et al., 1993**). Also Boulton et al.. have shown that important changes in the distribution and level of pressures under diabetic neuropathic feet occur during a relatively short time in the natural history of foot pressure abnormalities in neuropathic diabetic subjects (**Boulton et al., 1987**).

As regards variability of pressure loading, the neuro-ischaemic patients behaved similarly to the control groups suggesting a less variable gait than the neuropathic patients. This may be somehow surprising as the neuro-ischaemic patients also had a degree of neuropathy, although this was less advanced.

A possible explanation may be that the neuropathic patients with an advanced degree of neuropathy had lost their proprioceptive sensitivity almost entirely and they were more likely to be unsteady when walking and to traumatise their feet easier. However the neuro-ischaemic patients who had a lesser degree of neuropathy, may have been more congruous in the way they loaded the pressures and may have still been able to develop an antalgic gait in a consistent manner, as a normal control would do.

Conclusion

The neuro-ischaemic patients who tend not to develop ulcers under the plantar surface, but on the margins of the foot, have been shown to have abnormally high vertical foot pressures, but a consistent pattern of loading suggestive of a constant, normal gait in the presence of a comparable degree of neuropathy to the pure neuropathic patients. However this was not associated with plantar ulceration. This pattern of gait was similar to the diabetic controls and non-diabetic controls that had lower foot pressures. However the neuropathic patients, who tend to develop ulcers on the plantar surface of the foot, had high pressures, although lower than the neuro-ischaemic ones, but an inconsistent pressure loading pattern suggestive of a variable gait.

These findings may indicate different mechanisms of ulcer formation between neuro-ischaemic and neuropathic diabetic patients, possibly linked among other factors to the pressure distribution pattern.

Therefore the whole issue of ulceration in neuro-ischaemic patients raises new questions for future research as regards the time characterisation of pressures distribution inside the shoe, the size and role of shear stresses in foot ulceration, and the role of soft tissue characteristics in the aetiology of foot ulceration.

Chapter 5. THE EFFECT OF REGULAR CALLUS REMOVAL ON FOOT PRESSURES

5.1 Background

Clinical studies have reported ulcer formation to be invariably associated with plantar callus (**Edmonds et al., 1986**). A clinico-pathological study of diabetic foot ulcers in 54 patients during a 32-month period suggested that abnormal pressures contributed to all lesions occurring in areas of callus (**Jones et al., 1987**), which also took longer time to heal than traumatic lesions.

Haemorrhages have been found within plantar callus in a study of 100 diabetic patients with neuropathy (**Rosen et al., 1985**). Furthermore recent studies of magnetic resonance imaging in diabetic patients with a history of foot ulceration found artefacts or 'drop outs' on the image of the foot. These are thought to represent accumulation of haemoglobin degradation products in the soft tissues of the foot. Although the vertical plantar pressures were not different in patients with or without these soft tissue haemorrhages, the presence of such soft tissue haemorrhages might be a result of increased shear forces (**Brash et al., 1995**). Likewise they might reflect intrinsic capillary fragility which is associated with microangiopathy, highlighting once more the interaction between the microcirculation defects and the other risk factors implicated in the aetiology of foot ulceration such as callus formation and foot pressures. Furthermore the diminished hyperaemic response to noxious stimuli due to a reduced axon reflex in neuropathy plus abnormal neuro-vascular responses are likely to delay healing of lesions precipitated by minor or major trauma easily unnoticed by an insensitive foot due to neuropathy.

The reduction in dynamic plantar foot pressures, when the callus was removed in diabetic neuropathic patients, has proven also that the callus may act as a foreign body elevating the plantar pressures (**Young et al., 1992**) and predispose to foot ulceration. It also has highlighted the necessity of regular chiropody in the care of diabetic foot, which is of extreme importance in preventing foot ulceration and amputation according to the St. Vincent Declaration. Moreover a study evaluating a structured teaching and treatment programme including chiropody has shown the

significant decrease in the number of patients with callus formation and poor nail care, which was associated to a concomitant reduction in the health care costs due to the prevention of major health problems **(Pieber et al., 1995)**.

Therefore chiropody has been proven to be an essential aide in the care of the diabetic foot. The question arising next was:

- how often chiropody treatment should be performed, as the optimum frequency of callus removal is unknown.

Patients come on a regular basis to the Diabetic Foot Clinic in King's College Hospital for callus removal on the advice of the chiropodist treating them, who takes into account the different clinical variables such as history of ulceration, individual rate of callus formation and level of activity in each patient. However none of them are quantitative variables.

One way to assess quantitatively the effect of callus removal is to measure the plantar pressures, and most important inside the shoe, where the ulceration is more likely to occur in real-life conditions. Only one single study has been done previously, which tested the effect of callus removal on foot pressures, but it was performed barefoot. Nevertheless it has found an important reduction in plantar pressure of 25% when **(Young et al., 1992)** the callus was removed. However follow-up studies have not been performed, and it is important to elucidate what happens from the time when callus is removed until the patient presents again at the Diabetic Foot Clinic.

Aim of the study

Therefore the primary aim of this study was to quantify the change in plantar pressures before and after callus removal. In a pilot follow-up study the change in plantar pressures when the patient comes back next time for regular chiropody was measured in order to assess the efficiency and the necessity for frequent chiropody.

The F-Scan system of dynamic measurement of foot pressures inside the shoe was used in the study in an attempt to establish its value for determination of the suitable frequency of callus removal.

Also by weighing the callus and recording the time interval between chiropodial treatments we made an attempt to quantify the effect of chiropody.

5.2 Methodology and study conditions

Foot pressures assessment as described in the previous subchapter.

5.2.1 Protocol

The patients' feet were inspected for the presence of callus before the test and the area was noted for the attention of the chiropodist and to enable the investigator to locate it for F-Scan analysis. Patients had an F-Scan test before and after the callus was removed.

The amount of callus removed was placed in a sterile container labelled with the name of the patient, the date and the site where the callus was removed from, plus with the name of the chiropodist. The callus removed was kept in a dry container and weighed as dry-substance, at least 1 month after removal. In a preliminary pilot-study we found that the weight of callus at 1 month, 3 and 6 months after removal remains constant if kept in the same dry container.

5.2.2 Recording

Each patient walked wearing standard trainers on the same even area, for three runs, the last two runs being recorded. One new insole was used per patient.

5.2.3 Analysis

The plantar pressures were measured as peak pressures. The pressures were read from the pressure-time graphs for the area of interest by moving the cursor along the graph and choosing the point of maximum pressure. This was the area visible on the map of the foot which corresponded to the area where the callus was identified at foot inspection and from where the callus was subsequently removed. On the screen this area of interest was selected by placing the standard size ($0.25cm^2$) box on it and this was followed sequentially before and after callus removal and then again at follow-up.
The peak pressure was calculated as a mean of the three steps of the second recorded run, as a method to standardise the analysis at each visit.

Standard trainers were Clarks 'Swing Low' trainers with a standard inlay molded Plastazote (Polyethylene) foam with a small heel cup and arch support laminated to a woven nylon sock. A second layer of Polyurethane was used to improve the cushioning.

5.2.4 Neuropathy assessment

The presence of nerve damage was assessed in both lower limbs by clinical examination of the ankle reflexes and foot pulses, together with recording the vibration sensory threshold (VPT). Thermal sensory thresholds (TPT) were also recorded with a Thermal tester (Somedic, Stockholm, Sweden) from the dorsum of the foot and the response to five warm and five cold stimuli delivered at random time intervals was recorded.

5.3 Patients

The selection of patients was made taking into account 24 consecutive patients who came to the Diabetic Foot Clinic for regular callus removal. These patients were divided into three groups after the time interval between two visits at the clinic for callus removal:

Group 0 - 6 patients who presented for the first time ever for callus removal and who did not have a history of ulceration.

Group A - 9 patients who required chiropody treatment on a regular basis, at every 6-8 weeks and had a history of ulceration.

Group B - 9 patients who needed more frequent chiropody, at every 3-4 weeks and had a history of ulceration.

The assessment of plantar pressures was done in the 24 patients on the day of chiropody treatment before and after the callus removal. In 20 patients we were able to quantify the callus by weighing it as dry substance.

Table 5.1 Clinical and neuropathy details of patients

	Group 0	Group A	Group B
Patients	n=6	n = 9	n = 9
Age (years)	50.8±5.7	61.2 ± 3.9	69.2 ± 2.5
Diabetes duration (years)	11.3±4.4	24.6 ± 6.3	15.8 ± 4.3
Vibration perception threshold (V)	15.8±3.6	36.8 ± 3.7	31.7 ± 3.4
Thermal perception threshold for hot (°C)	8.5±0.6	12.2 ± 1.0	13.0 ± 0.9
Thermal perception threshold for cold (°C)	2.5±0.6	11.4 ± 1.8	9.9 ± 1.8
HbA1c (%)	8.1±0.7	9.2±0.9	9.8±0.5
Weight (kg)	79.1±6.2	86.5±6.5	76.3±2.0
Time interval between chiropody treatment (weeks)	never before	6.7±0.3	4.0±0.2

Mean ± SEM

In Group 0: 2 patients had callus under their first metatarsal head, 3 patients under the 2nd-3rd metatarsal heads, 1 patient under 4th metatarsal head.

In Group A: 5 patients had callus under their first metatarsal head, 2 patients under the 2-3 metatarsal heads, 1 patient under 5th metatarsal head and 1 patient under the Charcot deformity.

In Group B: 4 patients had callus under their first metatarsal head, 2 patient under the 3rd metatarsal head, 3 patients under 4-5th metatarsal heads.

Characteristics of the patients

All patients in Groups A and B had peripheral neuropathy and a history of neuropathic foot ulceration, whereas the patients in Group 0 had less neuropathy and no history of neuropathic foot ulceration. All groups of diabetic patients had a long duration of diabetes, although those in Group B had the longest duration of diabetes. The diabetes control was similar in all groups (Table 5.1). All the patients included in the study were free from major peripheral arterial disease: foot pulses were easily palpable and ankle: brachial ratios were > 0.8.

5.4 Follow-up pilot study methodology

In an attempt to prolong the interval between treatments 5 patients from Group B, who previously used to come at 3-4 weeks interval, were followed-up and the interval was increased to 6 weeks in 3 of them and 8 weeks in two of them. This was done in an attempt to assess if they needed frequent chiropody or longer time intervals may be a feasible and more cost effective, but still a safe option for callus removal in prevention of ulceration.

The plantar pressures before and after callus removal were re-assessed at the follow-up visits to the Diabetic Foot Clinic in order to correlate the increase in pressure with the built-up of callus after the initial removal.

5 patients from Group B were followed-up closely: 2 patients (W.G. and S.T.) were followed-up for 2 consecutive visits and 1 patient (W.J.) was followed-up for 3 consecutive visits; 2 patients (BD and J.I.) were followed-up for 4 consecutive visits.

3 patients were allowed to go 6 weeks, instead of their regular 3 or 4 weeks before chiropody. In 2 patients the subsequent interval was prolonged to 8 weeks in order to assess if longer time intervals lead to a proportional increase in pressure.

5.5 Statistical analysis

Mean and SEM were calculated using the statistical analysis Statwork package. Comparisons between plantar pressures before and after callus removal were made using the paired Wilcoxon Signed Rank non-parametric test and the Mann-Whitney test was used for comparisons between groups.

5.6 Results

Comparisons were made between the plantar pressures before and after callus removal in all patients (Figures 5.4 and 5.5). 5 patients from Group B were followed-up closely after their initial session of callus removal. In 3 patients who were allowed to go 6 weeks, instead of their regular 3 or 4 weeks before chiropody, the plantar pressures increased with 36.3±4.0%. In the 2 patients whose subsequent interval was prolonged to 8 weeks, the peak pressures have risen with 34.3±3.1%.

The follow-up patients from Group B were not included subsequently in the analysis of plantar pressures before and after callus removal of Group A.

5.6.1 Plantar pressures before and after callus removal in Group 0

The plantar pressures in patients who presented for the very first time to the Diabetic Foot Clinic were 374.8±69.9 kPa (Mean±SE) before callus removal and 251.0±56.0kPa afterwards, which indicates a decrease in pressure of 31.8±8.3%, p=0.014 with 341±156.5 mg callus removed. Figure 5.1

5.6.2 Plantar pressures before and after callus removal in Group A

The comparison between plantar pressures before and after callus removal in the Group A of patients who received regular chiropody at 6-8 weeks interval indicated a significant reduction of 29.0±4.2%, $p<0.005$. The peak pressures were 351.7±71.7kPa before the callus was removed and 240.5±48.4kPa afterwards. The callus weight was 467.8±83.6 mg. Figure 5.2

5.6.3 Plantar pressures before and after callus removal in Group B

When the plantar pressures before callus removal (241.0±29.9kPa) were compared to those (176.2±19.9kPa) after callus removal in the Group B patients who received frequent chiropody at 3-4 weeks interval, the mean reduction in pressure was 30.7±7.1%, $p=0.006$ and the weight of the callus removed was 276.5±75.9 mg. Fig 5.3

5.6.4 Comparisons between plantar pressure reduction in Group 0 and A and B

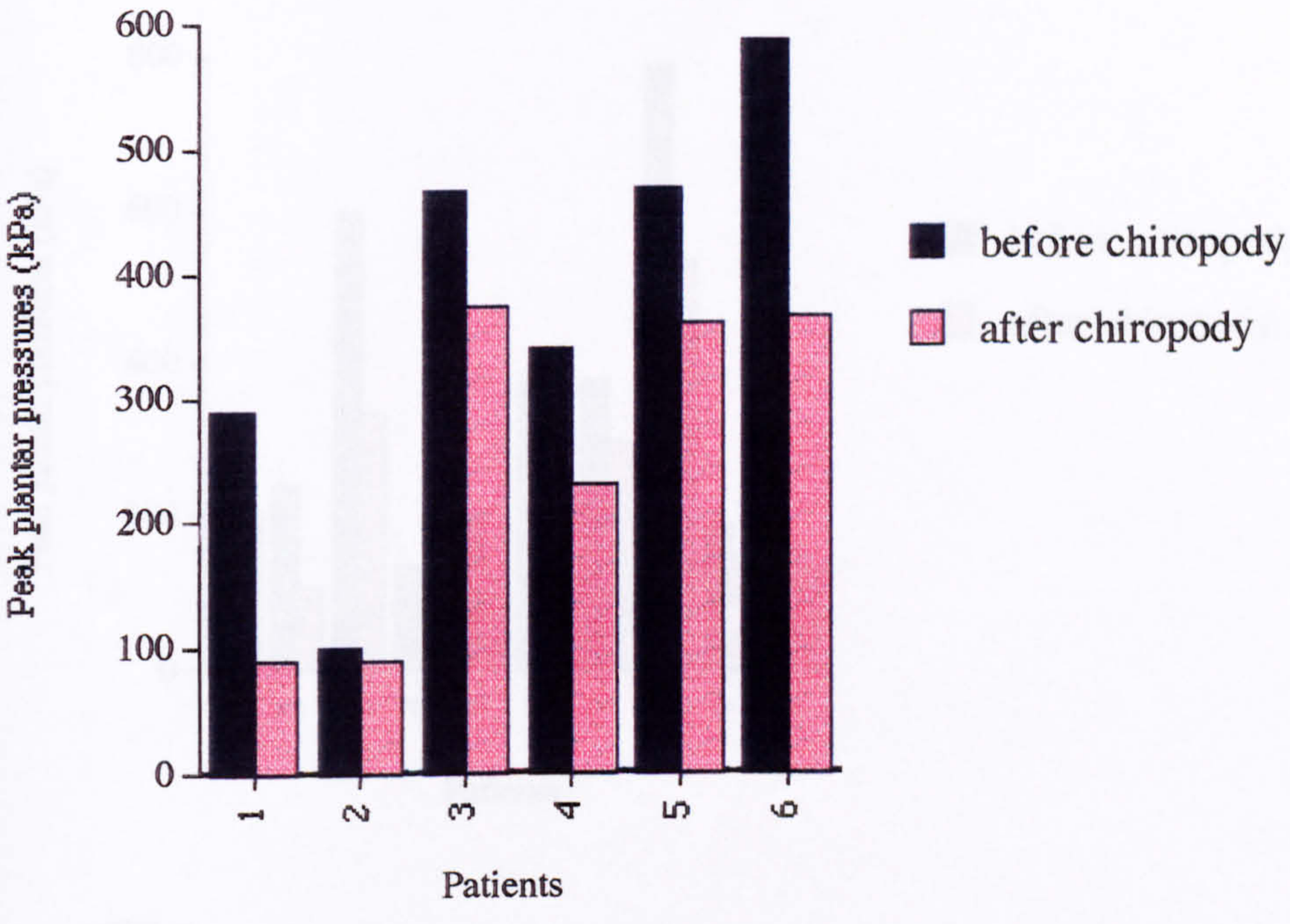
Although there was a different time interval between chiropody treatments there were no statistically significant differences between the percentage reduction in plantar pressures in the three groups. The weight of the callus removed was not statistically significant different in any of the three groups.

Table 5.2 Comparisons between the four groups of patients who had chiropodial removal of callus

	Group 0	Group A vs Group 0	Group B vs Group 0	Group A vs Group B
Patients	n=6	n = 9	n = 9	n = 9
Vibration perception threshold (V)	15.8±3.6	36.8 ± 3.7 p = 0.006	31.7 ± 3.4 p=0.004	p=0.49, NS
Thermal perception threshold for hot (*C)	8.5±0.6	12.2 ± 1.0 p=0.047	13.0 ± 0.9 p=0.01	p=0.44, NS
Thermal perception threshold for cold (*C)	2.5±0.6	11.4 ± 1.8 p=0.05, NS	9.9 ± 1.8 p=0.05, NS	p=0.48, NS
Plantar pressures (kPa) before callus removal	374.8±69.9	351.7±71.7 p=0.69, NS	241.0±29.9 p=0.10, NS	p=0.4, NS
Plantar pressures (kPa) after callus removal	251.0±56.0	240.5±48.4 p=0.70, NS	176.2±19.9 p=0.22, NS	p=0.49, NS
Callus weight (mg)	341.5±156.5	467.8±83.6 p=0.63, NS	276.5±75.9 p=0.78, NS	p=0.43, NS
Time interval between chiropody treatments (weeks)	never before	6.7±0.3	4.0±0.2	

Mean ± SEM

Fig. 5.1 Peak plantar pressures in Group 0 of patients who received chiropody treatment for the very first time



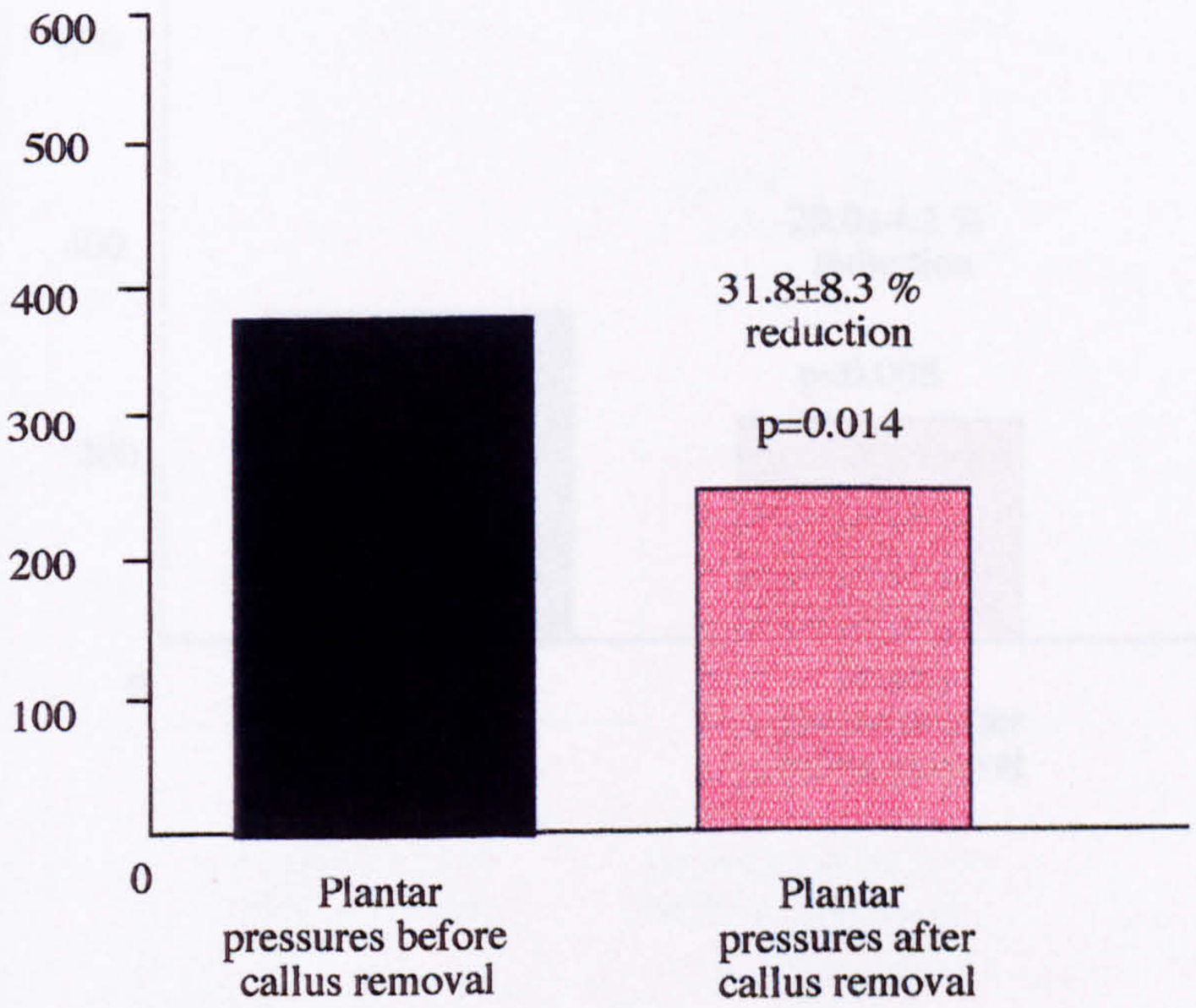
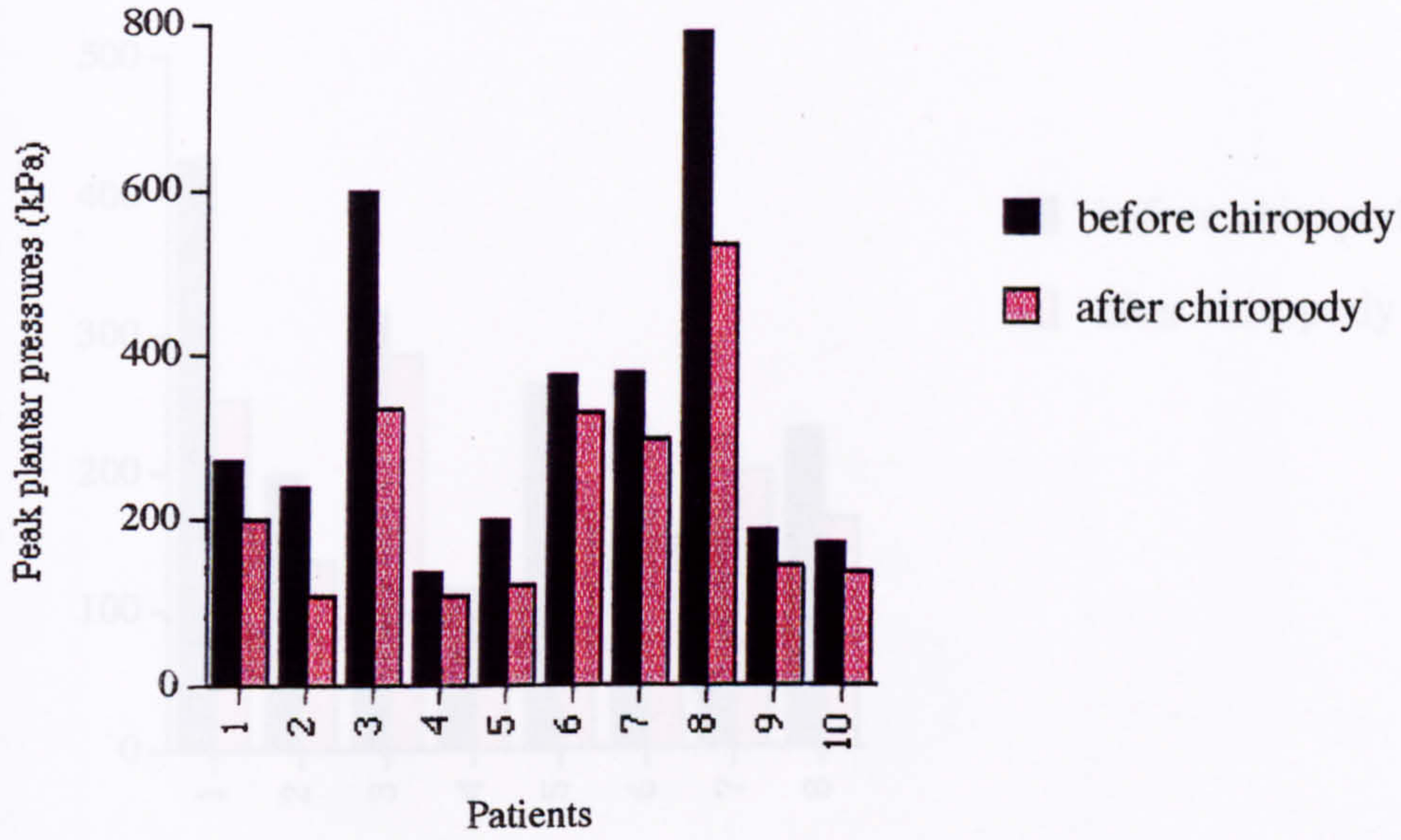


Fig. 5.2 Peak plantar pressures in Group A of patients receiving chiropody at 6-8 weeks interval



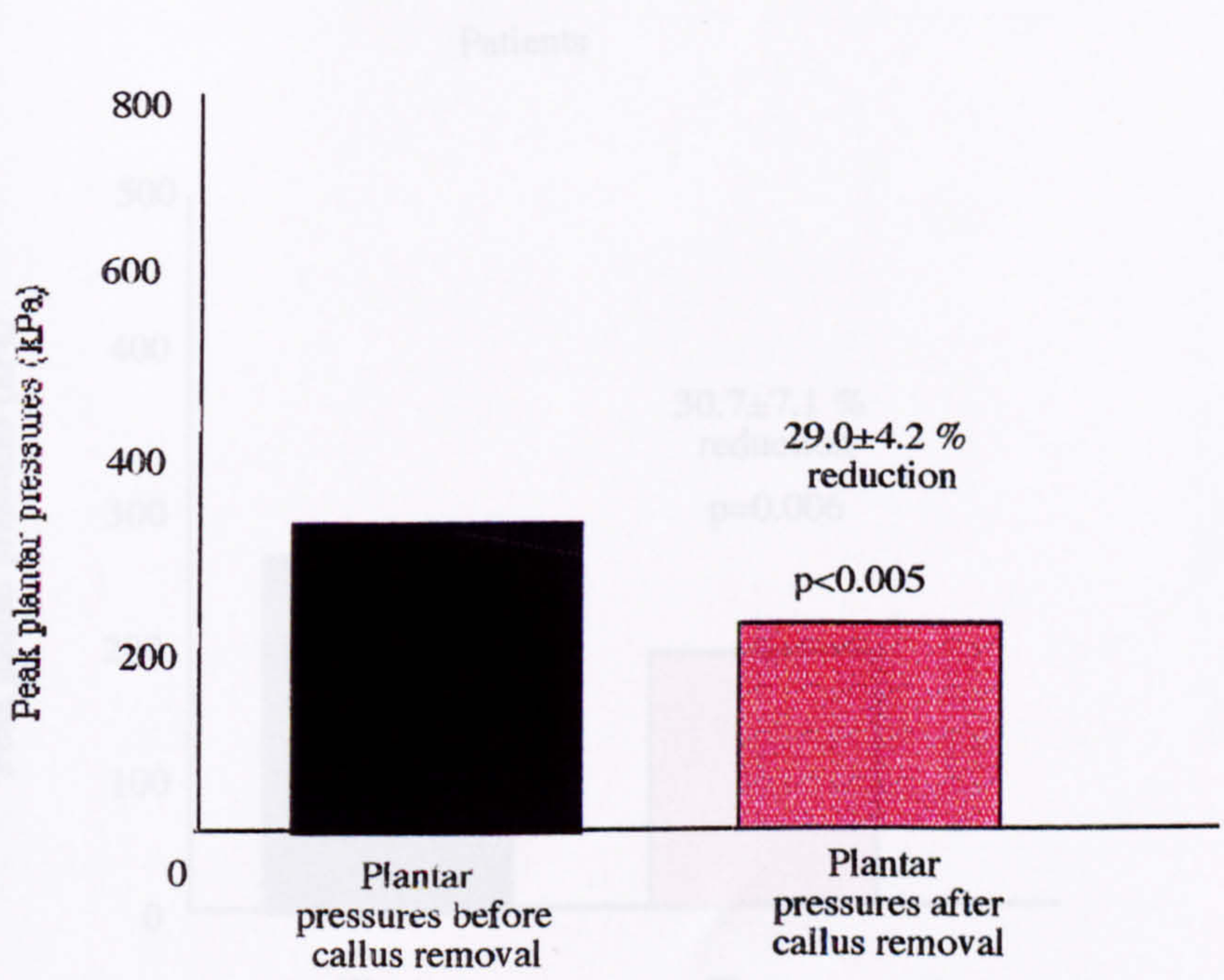
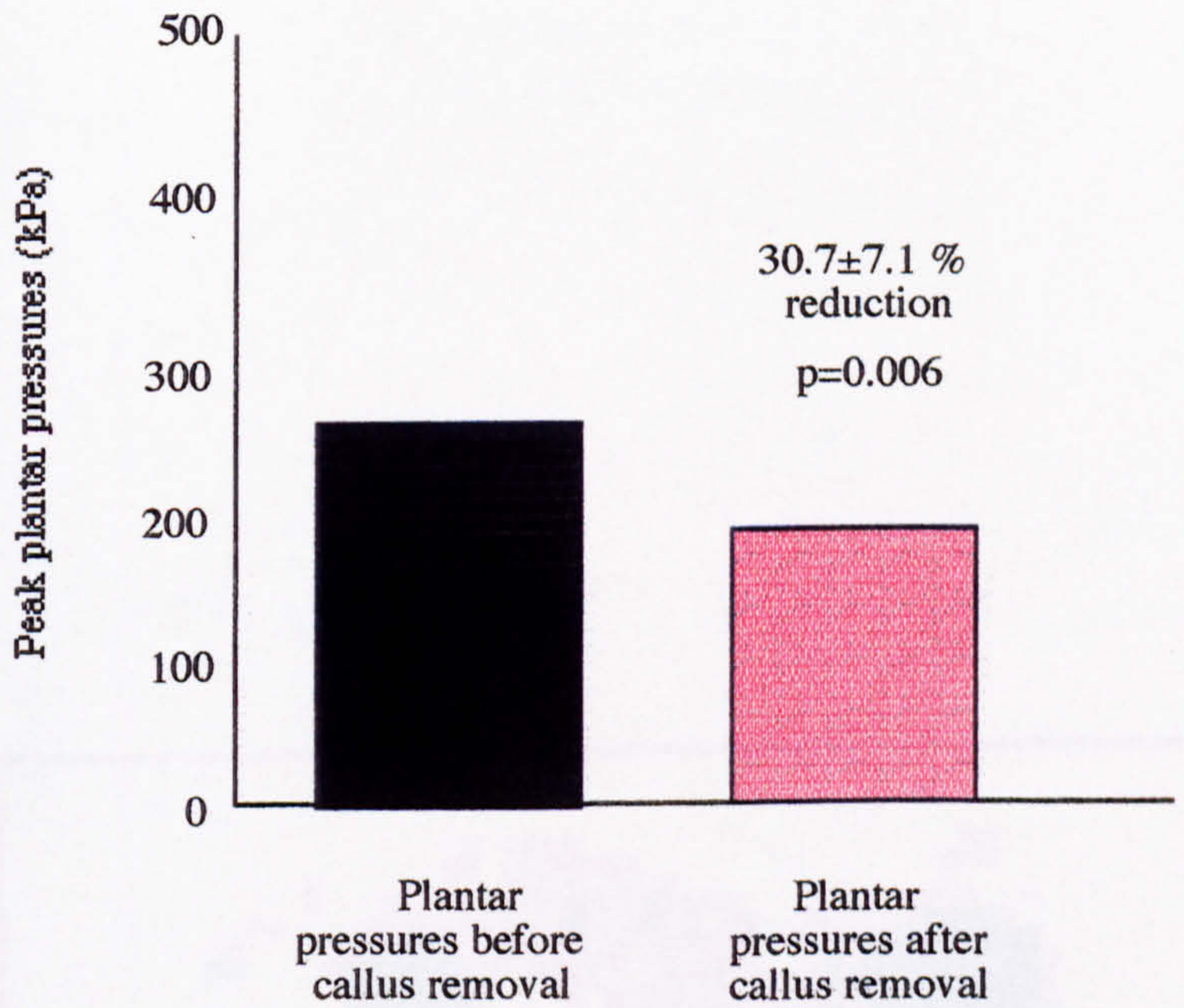


Fig. 5.3 Peak plantar pressures in Group B of patients receiving chiropody at 3-4 weeks interval



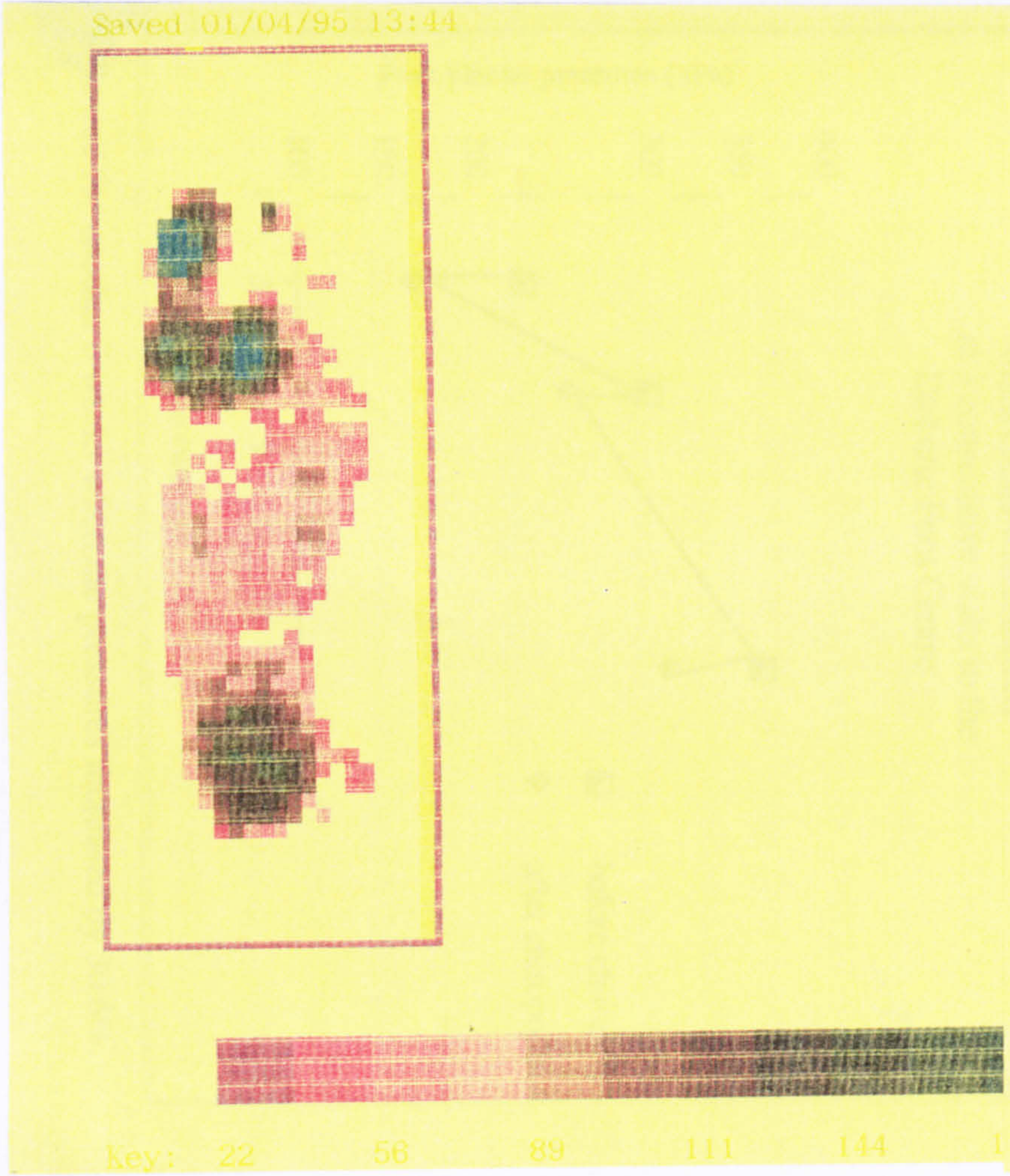


Fig. 5.4 Example of a F-Scan recording of plantar pressures **before** callus removal under first and second metatarsal

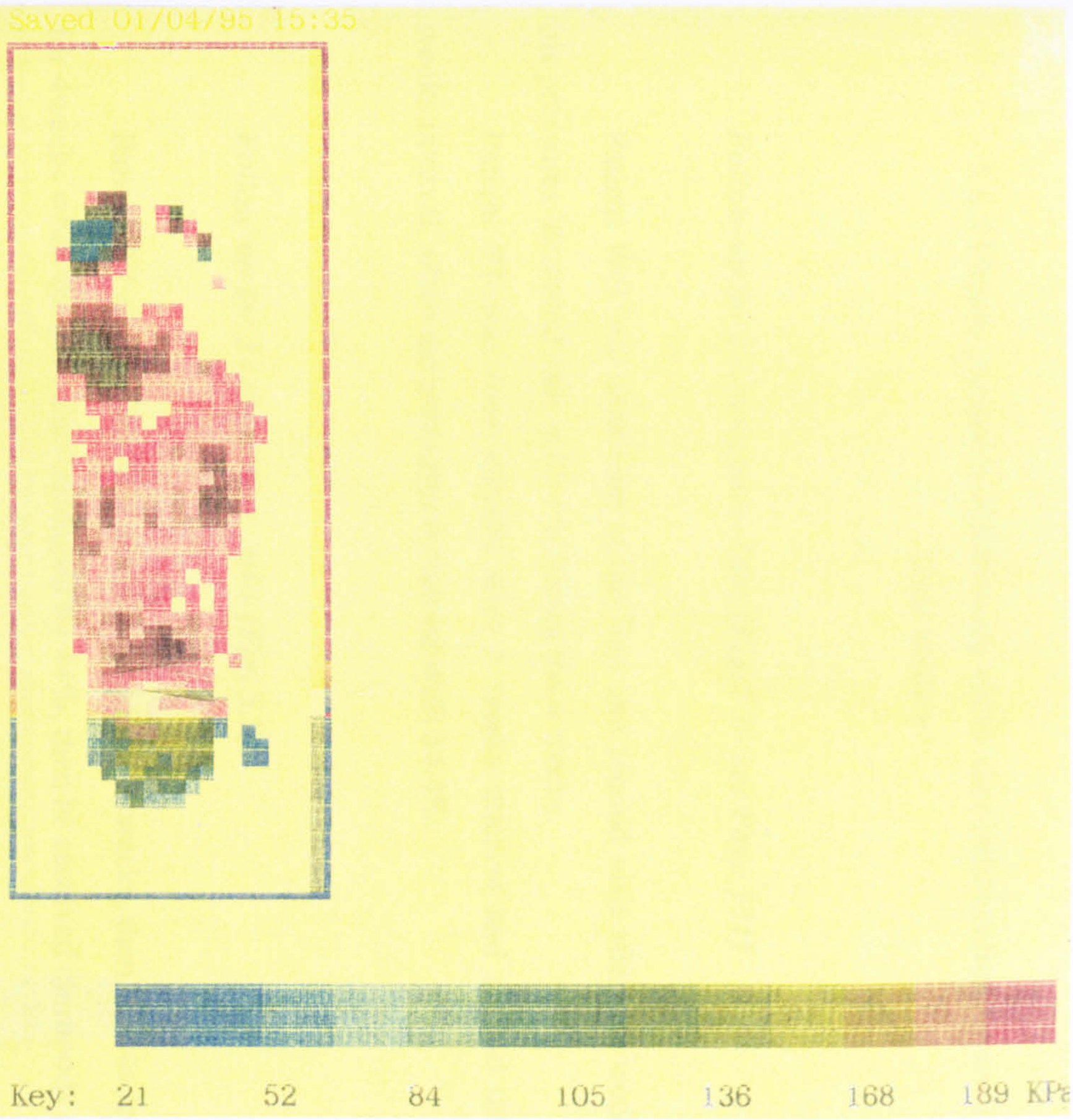


Fig. 5.5 Example of a F-Scan recording of plantar pressures **after** callus removal under first and second metatarsal

5.6.5 Plantar pressures at follow-up visits after initial callus removal

Case studies

Follow-up for 2 consecutive visits (Fig. 5.6- see Page 151)

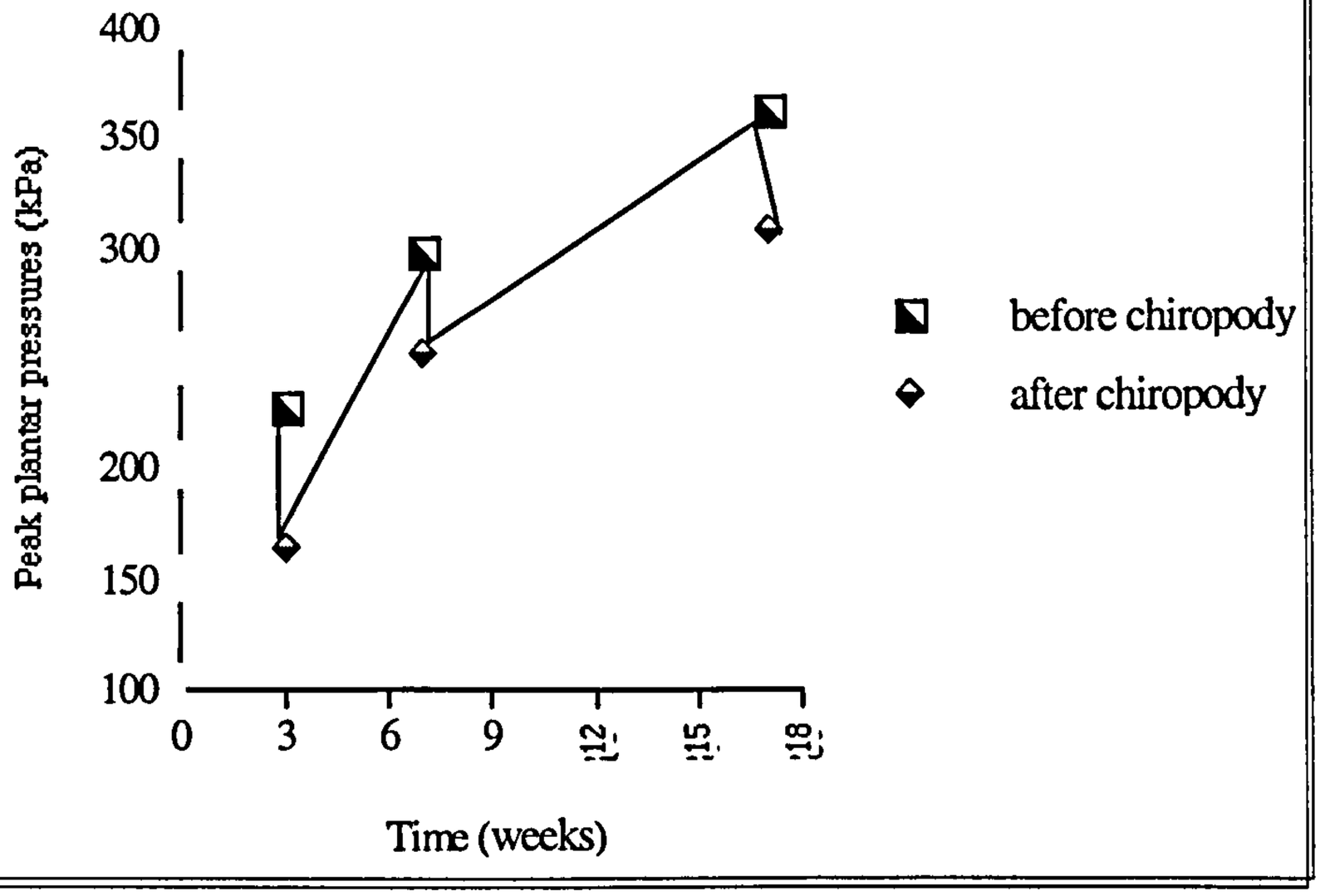
Patient WG was seen both at the first and second visit after a 4 week interval, his pressures increased only with 1% during the 4 weeks.

Patient ST was seen initially after 4 weeks interval and second time after 6 weeks interval, when the pressures increased with 34.4%.

Follow-up for 3 consecutive visits (Fig. 5.7)

Patient WJ came at his first assessment after a 3 weeks, then he was followed-up for 4weeks when the pressures increased by 44%, then he received chiropody and was

Fig. 5.7 Peak plantar pressures in patient W.J. when callus was removed at 3 consecutive visits to the Diabetic Foot Centre



followed for another 6 weeks when the pressures increased by 30.6%.

Follow-up for 4 consecutive visits (Fig. 5.8)

Patient BD came for the first assessment after 4 weeks interval, received chiropody and was followed-up for 8 weeks when the pressures increased with 37.5%, the callus was then removed urgently and she was followed-up for 6 weeks when the pressures increased by 28.1%, then she received chiropody and was followed-up for another 4 weeks when the callus did not build up.

Patient JI came after 4 weeks interval, received chiropody and was followed-up for 6 weeks when the pressures built-up by 44%, then for another 6 weeks when the pressures increased by 25.1%, then for 8 weeks during which the pressures increased by 31.2%.

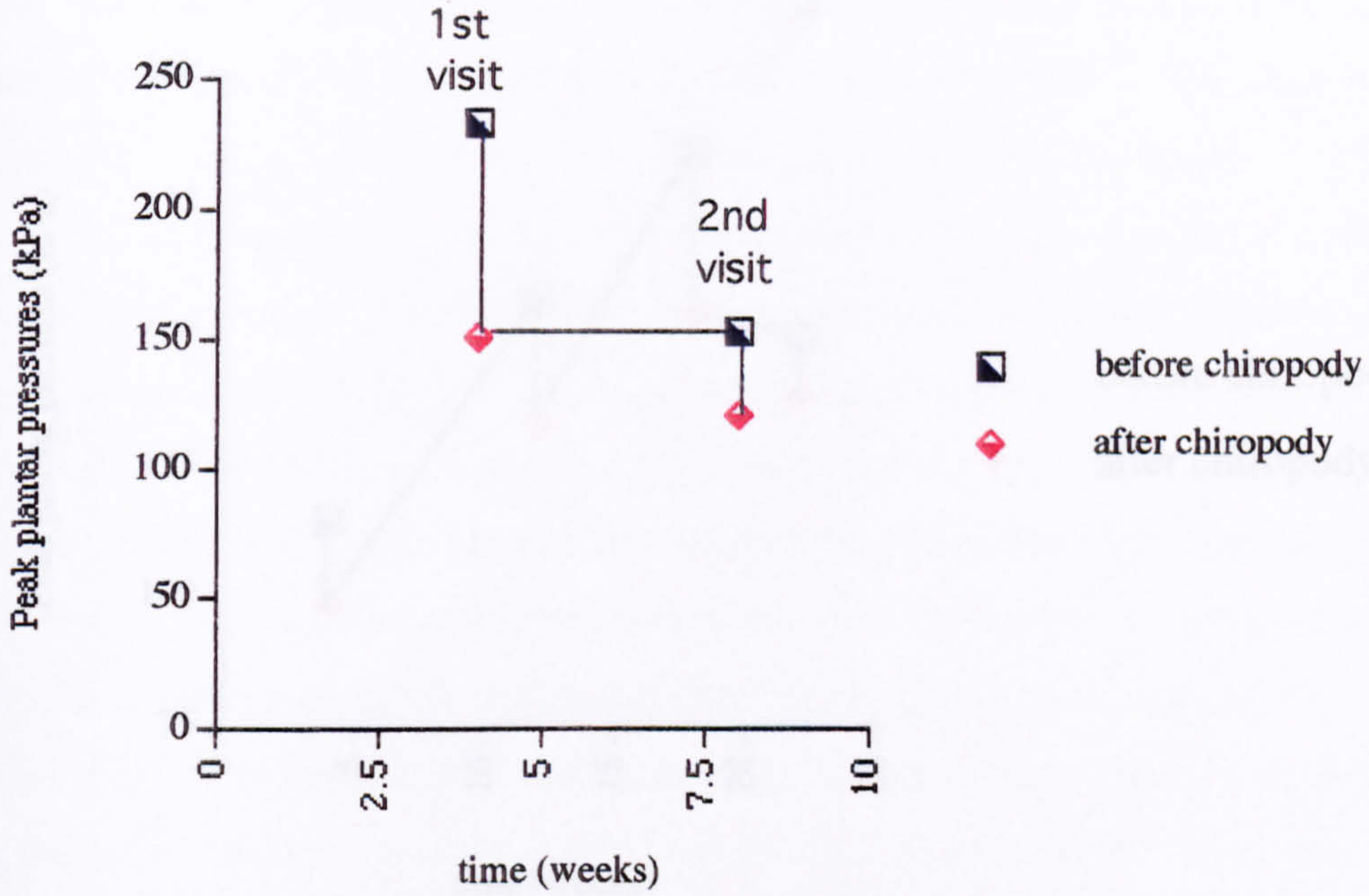
5.7 Discussion

Plantar callus is a common occurrence and is probably associated with high vertical and shear forces in neuropathic patients with insensitive feet. Shear stresses at these areas of high foot pressure could ultimately result in ulcer formation. Therefore the removal of callus by chiropody treatment is important in prevention of foot ulceration. Moreover methods to diminish callus formation are sought as an early preventative measure: a study assessing the use of orthotic devices to correct plantar callus in diabetic patients has shown the beneficial effect of orthotic devices in reducing the callus formation presumably by redistribution and reduction of pressure **(Colagiuri et al., 1995)**.

It is accepted that conventional regular chiropody is extremely important in preventing ulceration. The present study has shown that chiropody is an essential tool in callus removal leading to a significant reduction in plantar pressures of 31.8±8.3% in patients at their first ever visit to chiropodist, of 29.0±4.2% in patients requiring regular chiropody at 6-8 weeks time interval and of 30.7±7.1% in those coming more frequently at 3-4 weeks interval. Therefore independent of the time interval between treatments, the actual chiropodial technique of callus removal has an overall decreasing effect on the plantar pressures around 30%.

Fig. 5.6

Peak plantar pressures in patient W.G.
at 2 consecutive visits
at Diabetic Foot Clinic



Peak plantar pressures in patient S.T.
when callus was removed
at 2 consecutive visits to the
Diabetic Foot Clinic

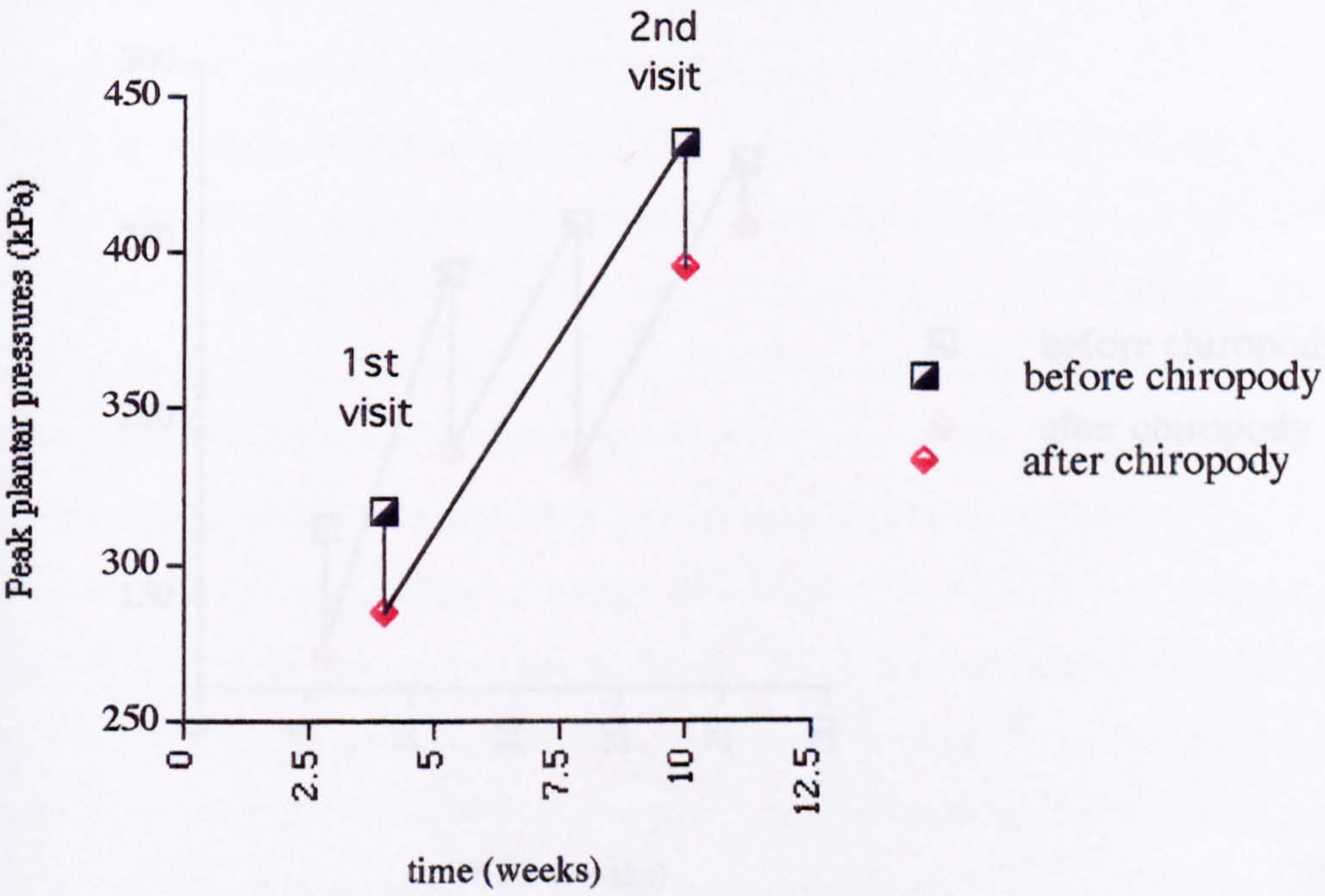
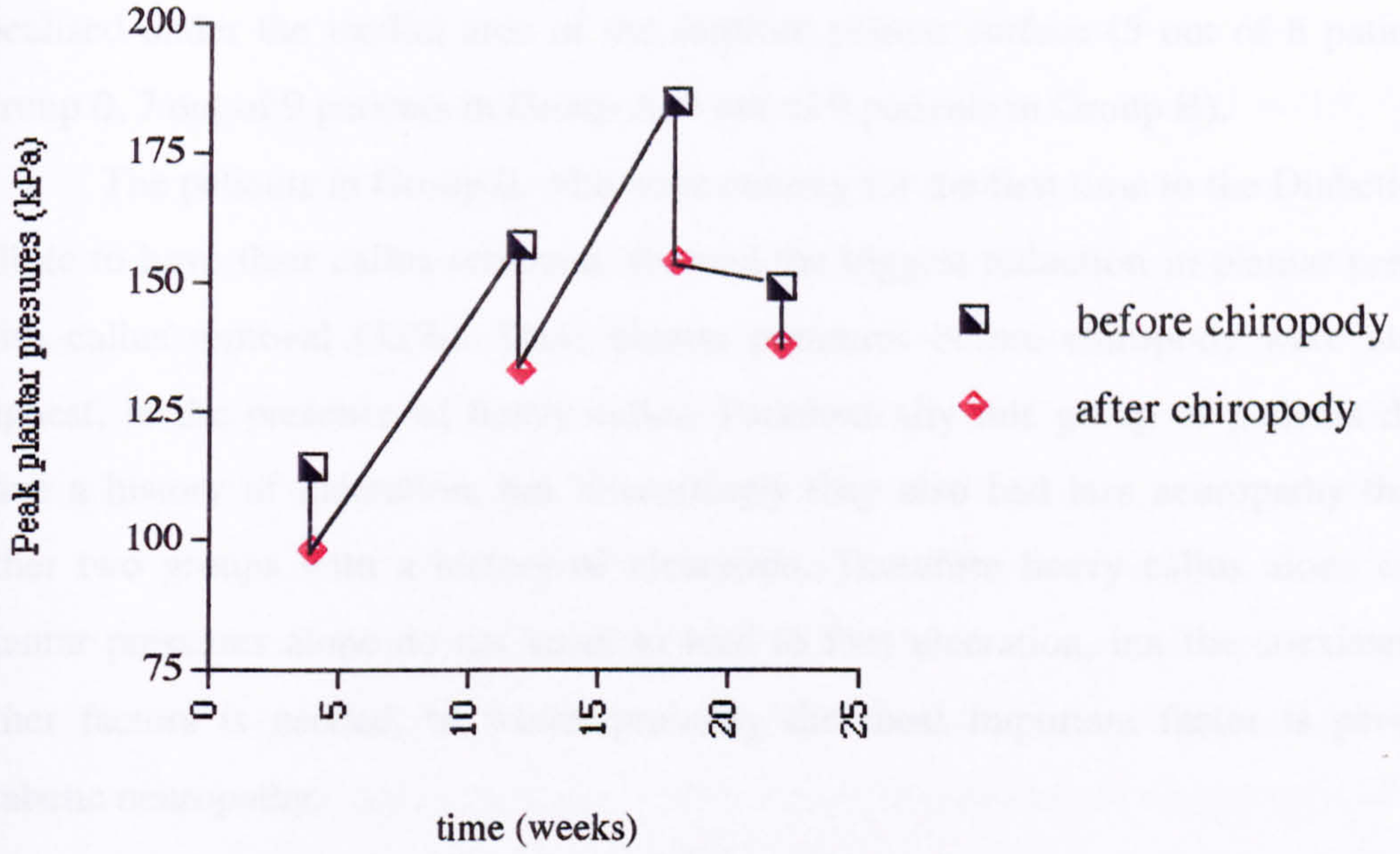
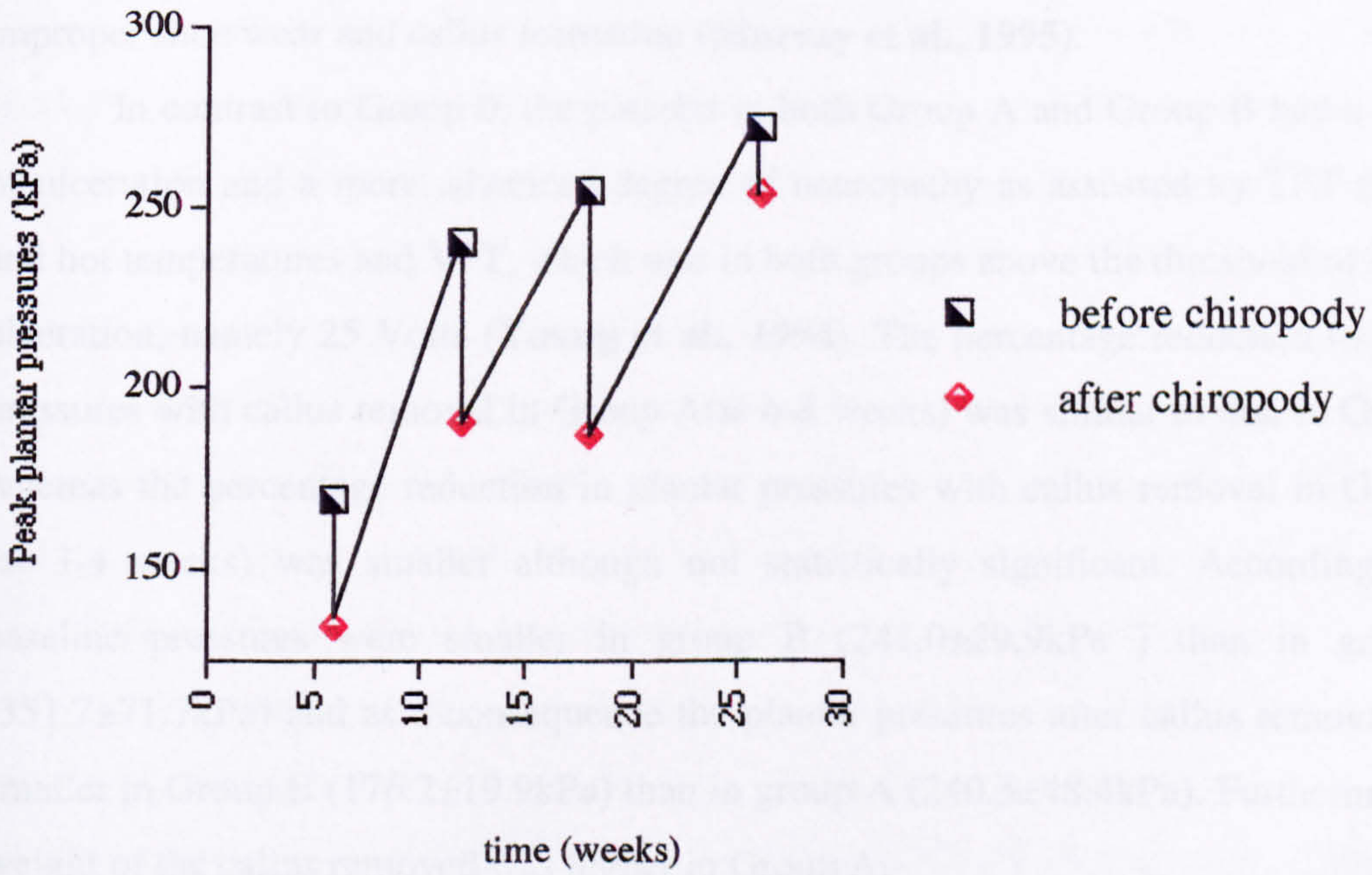


Fig. 5.8

Peak plantar pressures in patient B.D.
when callus was removed
at 4 consecutive visits to the
Diabetic Foot Clinic



Peak plantar pressures in patient J.I.
when callus was removed
at 4 consecutive visits to the
Diabetic Foot Clinic



This is in agreement with a previous study of callus removal in 17 diabetic neuropathic patients which showed that the peak pressures under 43 areas of callus in the forefoot fell by 26% after callus was removed. It was also demonstrated that the pressures under the heel were unchanged, highlighting the importance of assessment of specific areas of pressure as callus tends to be more localised in the forefoot.

Furthermore the present study has found that areas of callus were predominantly localised under the medial area of the forefoot plantar surface (5 out of 6 patients in Group 0, 7 out of 9 patients in Group A, 6 out of 9 patients in Group B).

The patients in Group 0, who were coming for the first time to the Diabetic Foot Clinic to have their callus removed, showed the biggest reduction in plantar pressures with callus removal (32%). Their plantar pressures before chiropody were also the highest, in the presence of heavy callus. Paradoxically this group of patients did not have a history of ulceration, but interestingly they also had less neuropathy than the other two groups with a history of ulceration. Therefore heavy callus alone or high plantar pressures alone do not seem to lead to foot ulceration, but the coexistence of other factors is needed, of which probably the most important factor is peripheral diabetic neuropathy.

These findings support those of **Fernando et al. (1991)**, who also showed that abnormal plantar pressures alone do not lead to foot ulceration. Furthermore they come into accord with the multi-factorial theory of diabetic foot ulcer aetiology **(Boulton, 1994)** including: neuropathy, limited joint mobility, high foot pressures, trauma, improper shoe wear and callus formation **(Murray et al., 1995)**.

In contrast to Group 0, the patients in both Group A and Group B had a history of ulceration and a more advanced degree of neuropathy as assessed by TPT for cold and hot temperatures and VPT, which was in both groups above the threshold of risk for ulceration, namely 25 Volts **(Young et al., 1994)**. The percentage reduction in plantar pressures with callus removal in Group A(at 6-8 weeks) was similar to that in Group 0, whereas the percentage reduction in plantar pressures with callus removal in Group B (at 3-4 weeks) was smaller although not statistically significant. Accordingly, the baseline pressures were smaller in group B (241.0±29.9kPa) than in group A (351.7±71.7kPa) and as a consequence the plantar pressures after callus removal were smaller in Group B (176.2±19.9kPa) than in group A (240.5±48.4kPa). Furthermore the weight of the callus removed was higher in Group A.

Although not statistically significant, these differences in pressure might highlight the clinical importance of the absolute levels of pressure attained by regular chiropody in prevention of ulceration and suggest the 3-4 week interval between visits as being suitable for control of callus formation and prevention of ulceration.

The trend towards higher pressures and the higher values of callus weight in Group A receiving regular chiropody at 6-8 weeks interval might suggest that these patients simply needed more frequent chiropody.

However with no recurrence of ulceration in this, admittedly small, group of patients seen at 6-8 weeks interval, another explanation could be that: those patients coming at 3-4 weeks might be coming too often to the chiropodist, with no real benefit. They could be asked to come at longer time intervals allowing a better use of the time and staff resources in the Diabetic Foot Clinic. Alternatively, it could be argued that the higher range of pressure at 6-8 weeks interval is still safe regarding ulceration, but only in those patients characterised by a slower rate of callus formation.

In the follow-up case studies, the rate of callus formation varied in different individuals probably related to their level of activity and mobility. In two instances in 2 of our follow-up patients (diagrams) there have been no significant increase in pressure at 4 weeks after callus removal, whereas another patient increased his pressures with 44% in 4 weeks. However as the increase in plantar pressures after 8 weeks was not much higher than that after 6 weeks, from these observations it seems that the rate of callus formation rises sharply initially in the first 4-6 weeks and then the rate of callus formation and pressure increase slows down. However it has been demonstrated that even moderate stress, if it is repetitive could lead to soft tissue breakdown and ulceration (**Brand, 1988**), with the necessity of callus removal sooner (at 6 weeks) than later (at 8 weeks).

This may be of importance in the Diabetic Foot Clinic in deciding how frequently a patient ought to be seen in correlation with his plantar pressures. Although now empirically determined by chiropodists by the absence of recurrent ulceration, the frequency of callus removal might be dictated by the individual rate of callus formation which can be now quantified by measuring the increase in plantar pressure with the built-up of callus. In addition from our follow-up cases it was clear that although the pressure decrease with callus removal tended to be in a certain range per patient (e.g. patient BD: 14-15-17% or patient JI: 21-17-26%), there is some variability in the amount of callus removed and sometimes in the actual pressure reduction (BD: 7.3% or JI: 4%); all these

are probably related to differences in the operating techniques of the chiropodists. These would influence the immediate result, the weight of callus removed, which previously was thought to be a useful indicator of the efficacy of callus removal. However the measurement of plantar pressures has proven to be a more functional and objective indicator valuable in the assessment of chiropodial treatment.

Conclusion

The F-Scan methodology can provide the facility to follow-up the callus formation until it reaches the upper limits of acceptable pressure and requires removal. This might prove of benefit for reducing the costs of foot care by reducing the frequency of chiropodial treatment and making it more cost-effective.

Using this relatively recent technology, longitudinal studies of plantar pressure in correlation with chiropodial follow-up are needed now in a larger number of patients. Previous longitudinal measurements of plantar pressure have shown a change in the pressure distribution but with no significant rise in the peak forefoot pressure when performed barefoot **(Boulton et al., 1987)** or in contrast, an increase in vertical pressures was reported in neuropathic patients with high plantar pressures which were considered to be highly predictive of subsequent plantar ulceration **(Veves et al., 1992)**.

The measurement of foot pressures may prove to be useful first for the 'on the spot' assessment of the efficacy of the callus removal and secondly in the chiropodial follow-up of the patients. Diagrams such as those drawn for our follow-up case studies could be included in the notes of the patients coming to the Diabetic Foot Clinic in order to provide the necessary documentation regarding the change in plantar pressure before and after chiropody at each visit.

These observations of plantar pressures are of interest, but further close follow-up of a larger number of patients is required, preferably a weekly measurement of plantar pressures to assess the rate of callus formation and to define in a larger number of patients the threshold of pressure for the removal of callus in order to keep the diabetic foot free from ulceration.

Chapter 6. THE EFFECT OF FITTED SHOEWEAR ON FOOT PRESSURES

6.1 Introduction

Footwear is an important aspect of the treatment of diabetic foot and the aim of this study was to assess the quantitative effect of different types of footwear on foot pressures.

6.1.1 Role of prescription footwear in prevention of foot ulceration

The role of prescription footwear in prevention of recurrent ulceration is achieved by counter-acting the mechanical factors involved in ulcer formation; namely by accommodating the deformed foot, supporting the insensitive foot with limited joint mobility and decreasing the high foot pressures.

The moulded inserts of the prescription shoes are thought to have two main effects on plantar pressures:

- first to reduce the foot pressures directly through the cushioning effect of different types of materials used for their inserts,

- secondly to redistribute the pressures through the moulding process of inserts to fit the characteristics of the foot. Therefore the vertical forces would be dispersed from small areas of high pressure on the larger surface of the sole with a subsequent reduction in pressure.

6.1.2 Characteristics of prescription footwear

Tovey's **(Tovey, 1984)** guidelines regarding the role of prescription footwear require that the shoes should be able:

- to accommodate foot deformities
- to stabilise foot deformities
- to limit aberrant joint motions
- - to relieve the excessive foot pressures
- to reduce shock and shear

The shoes ought to be of sufficient depth to accommodate the foot to avoid undue pressure from the upper side of the shoe. The actual process of shoe fitting requires that:

- both feet should be measured
- shoes should be fitted on both feet during weight bearing
- the proper position of the first metatarsal should be checked
- the correct length and width should be provided
- the heel should be supported
- a proper fit over the instep should be checked.

Most orthotists and surgical shoes manufacturers tend to use soft leather for prescription shoes with a large upper to accommodate the often deformed foot, and an extra strip of leather around the heel to keep it secure. Inside the shoe, seams are avoided in the areas prone to friction. More recently elasticised bands (Recco) or materials such as Dupont material, which has elastic and stretch properties are used to accommodate the toes. In the case of the hammer toes, some manufacturers heat the leather according to the position of the hammer toe in order to stretch out the upper and allow more space and flexibility **(Uccioli, 1996)**. As usual the sole has a shank to make it rigid and able to support an insensitive foot with wasted interosseous muscles.

Ultimately the prescription shoes offer a way to accommodate both the deformity and the insert. The latter is the most important component of the shoe as regards provision of necessary cushioning. The insert is often multi-layered and can be up to 8 mm thick **(Tovey, 1984)**.

Prescription shoewear can be divided into two groups: stock shoes or bespoke shoes. Therefore prescription shoes although coming in a large range of styles and designs, have usually extra-depth, whether they are manufactured stock shoes such as the 'New Style TM' with a Poron insert (Ken Hall Ltd, Kettering, Northants.) or bespoke shoes such as those provided by the Orthotic Dept. at King's College Hospital and containing ethyl-vinyl acetate (EVA) inserts.

Similarly there is an enormous variation between the type of inserts and the materials used in their manufacture, with different characteristics as regards their amount and rate of mouldability and permanent deformation and hence in their ability to provide cushioning, and/or shock absorption **(Brodsky et al., 1988)**. Some inserts are made of resilient, semi-rigid materials (Poron) good for shock absorption **(Pratt et al., 1986)** and foot control, but they are usually flat and not moulded on the sole of the foot.

Other inserts are made of soft materials such as EVA polymer, which are comfortable, inexpensive, easily adjusted being mouldable and allowing better cushioning **(McKenzie et al., 1985)**, but there is the risk of flattening of the material **(Garcia et al., 1994)**. The ideal insert represents a combination of materials to achieve both durability and mouldability **(Brodsky et al., 1988)**. The actual design of the inserts could also have a direct effect on foot pressures. For example the mid-sole construction often found in running shoes (trainers) with moulded inserts has a beneficial effect by redistributing and reducing the plantar pressures.

Prescription of fitted footwear still involves a series of empirical stages **(Lord, 1989)**. When shoes are to be fitted, the physician suggests a standard design or individually designed bespoke shoes. Matching the surgical shoes to the individual characteristics of the foot requires special insoles designed with the skills of an orthothist, which makes them expensive. The shoes are produced through a series of fitting sessions with costly materials and the demand of fitted footwear on the hospital budget can be substantial. From the £38 million annual NHS budget, 30% is spent on foot orthoses and footwear **(Fox et al., 1994)**. Thus, in the past, the absence of techniques for in-shoe foot pressure measurements have made the assessment of footwear difficult.

The F-Scan system is particularly advantageous for assessing the effect of different shoes on plantar pressures because it has an ultrathin insole, which can be placed inside any shoe and trimmed to the size and the shape of the shoe without interfering with the foot pressures.

6.1.3 Technical limitations of in-shoe plantar pressure assessment in relation with prescription footwear

Attempts to measure the effect of different footwear on foot pressures have been made previously, but they have had to take into account the technical limitations of the systems used for the assessment of plantar pressures. The limitations of the instrumentation with cumbersome techniques, measurement variability and inadequate durability, are the most important factors which have delayed the quantitative assessment of a variety of shoe wear on the foot pressures.

The in-shoe pressure transducer used to assess the effect of the rocker-bottom shoe on foot pressures had a number (72) of pressure-sensitive elements which could not cover all the areas of the foot and therefore certain areas of the foot were not monitored **(Cavanagh, 1990)**

In another study, using a smaller number of sensors (15 pressure-sensor insole) to measure the plantar pressures in 13 different shoes, considerable variability in the measurements of forefoot pressure was reported **(Schaff et al., 1986)**. These studies with discrete transducers have produced a variety of results when comparing prescription to conventional footwear ranging from 50% reduction to no change or to actual increase in some locations.

This highlights the necessity for a pressure-sensitive device containing numerous sensors to cover the entire area of the foot. This would not only provide the required spatial resolution, but also the possibility to detect the areas of highest pressure on the map of each individual foot. From this point of view, the F-Scan could be advantageous: its insole consists of 960 individual sensor cells, in a grid-like configuration, allowing a high spatial resolution. It is also ultrathin (1.8mm) and can be cut to the size and shape, often unusual, of the diabetic prescription shoes. However the fact that the insole has a limited life-time as described in the previous subchapter and there is a variability between the ability of different insoles to measure pressure **(Rose et al., 1992; Brown, 1996)** , limits its use. Nevertheless if one insole is used per patient useful comparisons can be made, especially in a study comparing the pressures of the same patient in different footwear. Therefore the design of the present study followed the methodology developed previously to reduce variability and provide reliable measurements.

A previous study using the F-Scan for in-shoe pressure measurements in diabetic patients with at-risk feet and in healthy subjects showed that the in-shoe pressures are significantly lower than the barefoot ones and that the shoes of diabetic patients provided a higher pressure reduction than did those of the control group; it concluded that the F-scan system can be particularly useful in assessing and designing footwear suitable for diabetic patients with at-risk feet **(Sarnow et al., 1994)**

6.2 Aim of the study

The primary aim of the present study was to assess the quantitative effect of different types of footwear on foot pressures in patients with recurrent ulceration, in a clinical situation characteristic for the Diabetic Foot Clinic in King's College Hospital.

The dynamic in-shoe foot pressures were measured in patient's own shoes, in standard trainers and in prescription shoes fitted with moulded ethyl-vinyl-acetate (EVA) or Poron inserts. As it is not possible to standardise what it is routinely done in the Diabetic Foot Clinic, we had to accept that patients commonly wear a wide range of shoes. Also the bespoke shoes could not be identical in all patients, being individually designed and made to measure for each of them. In an attempt to reduce the variability, all the assessed bespoke shoes were newly fitted, the standard trainers were nearly new, being used just for testing and not showing any signs of wear. However the patients' own shoes had different degrees of wear.

In a pilot study, 3 patients who were prescribed bespoke shoes with EVA inserts, were followed-up over 2 further visits.

Therefore our aim was to establish the value of different types of footwear in a group of patients with recurrent foot ulceration in the clinical setting of routine diabetic foot care as they presented to the Diabetic Foot Clinic.

6.3 Patients and methods

6.3.1 Selection of patients

The selection of patients was made by taking 25 consecutive patients attending the Diabetic Foot Clinic for whom prescription shoes or trainers had been recommended. These patients wore a highly varied mixture of their own shoes: including High Street shoes, patients' own trainers, used bespoke shoes with EVA inserts and used stock orthopaedic shoes with Poron inserts.

The assessment of plantar pressures was done in 21 patients on the day they received newly fitted prescription shoes (17 containing EVA inserts and 4 containing Poron inserts).

In the 21 patients:

- two did not have their 'own shoes' (which consisted of used prescription shoes left in the Orthotic Department to be repaired).

- two others had very deformed feet and they were unable to use the standard trainers provided by the Diabetic Foot Clinic.

Therefore a group of 19 patients could be used for comparison of new prescription shoes to own shoes and another (overlapping) group of 19 patients would be used for comparison of new prescription shoes to standard trainers.

In 17 patients common to the two groups, the plantar pressures measured in standard trainers were compared to those in patient's own shoes. In a further 4 patients who were considered but not provided with fitted shoes, plantar pressures were measured in their own shoes, and compared to those in standard trainers.

Patients in the follow-up pilot study

Three patients wearing prescription shoes with EVA inserts were taken into the follow-up pilot study. Details in Table 6.5.

In one patient (IT), a 54 years old male, with insulin-dependent diabetes of 50 years duration; weight of 81kg, height 186cm, the foot pressure measurements in bespoke shoes with EVA inserts were done in three occasions.

6.3.2 Characteristics of the patients

All patients had peripheral neuropathy and a history of neuropathic foot ulceration. Their mean age was 59.3±2.5 years. Two patients who did not have diabetes, but had spina bifida with a history of recurrent neuropathic ulceration were also included. Table 6.1

Table 6.1 Clinical details of patients

Patients	n = 25
Age (years)	59.3 ± 2.5
Diabetes duration (years)	19.6 ± 3.7
IDDM/ NIDDM	9 IDDM / 14 NIDDM 2 non-diabetic neuropaths
Vibration perception threshold (V)	35.3 ± 2.7
Thermal perception threshold for hot (°C)	10.3 ± 1.0
Thermal perception threshold for cold (°C)	8.2 ± 1.1

Mean ± SEM

The 23 diabetic patients had a long duration of diabetes, 19.6±3.7 years. There was a predominance of NIDDM patients. The patients included in the study were free from major peripheral arterial disease: foot pulses were easily palpable and ankle-brachial ratios were > 1.

6.3.3 Methodology and study conditions

Dynamic in-shoe foot pressures measurement using the F-Scan system was done as described and recommended in Chapter 3.

Protocol

All the pressure measurements in a patient wearing different types of shoes were done on the same day. Patients taking part in the follow-up pilot study were also tested during consecutive visits to the Diabetic Foot Clinic.

Recording

Each patient walked on the same even surface, for three runs, the last two runs being recorded in each type of shoe. The recording in each type of shoe was done in no particular order. One new insole was used per patient and it was placed inside the shoe of the foot, which had suffered recurrent ulceration in the past.

Analysis of pressure recording

The pressures in the three different type of shoes were measured as peak pressures. The area of interest was selected by placing the ($0.25cm^2$) box on the area of highest pressure visible on the map of the foot, which was followed sequentially in different types of shoes.

The pressures were read from the pressure-time graphs for the area of interest by moving the cursor along the graph and choosing the point of maximum pressure. The peak pressure was calculated as a mean of the three steps of the second recorded run, in order to standardise the analysis in each type of shoe.

Shoes

Patient's own shoes were tested. They come in a variety of styles and shapes.

Patients came to the Diabetic Foot Clinic wearing 4 main types of own shoes:

- High Street shoes with leather sole
- used bespoke shoes with EVA inserts
- used 'New Style TM' (Ken Hall, Kettering, Northants.) stock shoes with Poron inserts
- own trainers

Bespoke shoes fitted with ethyl-vinyl-acetate inserts were moulded by the Orthotics Company after the cast taken by the hospital Orthotics Department according to the individual characteristics of the foot. Layers of EVA, each having a different density were placed as follows in order to match the cast and provide adequate cushioning: the top layer had a Low Density EVA, followed generally by 2-4 layers of Medium Density EVA, finally the base layer was made of High Density EVA, the most dense and rigid layer aimed to fit a flat soled shoe.

Fig. 6.0 Example of bespoke shoe fitted with ethyl-vinyl-acetate (EVA) insert

In some instances if an extra internal rocker was needed, a layer of High Density black Plastazote was added. The number of layers of EVA were determined by the shape of the foot and its contours i.e. a cavus foot will need more layers than a less deformed foot to match the cast.

'New Style' stock shoes (Ken Hall, Kettering, Northants.) were stock extra-depth shoes manufactured in different sizes and fitted with a flat 2*3 mm Poron insert.

Standard trainers used in this study were Clarks 'Swing Low' trainers with a standard inlay moulded Plastazote (Polyethylene) foam and a second layer of Polyurethane used to improve the cushioning, with a small heel cup and arch support laminated to a woven nylon sock.

Methodology of follow-up pilot study

In order to assess the behaviour of EVA insert with time, repeated peak pressures measurements were performed in 3 patients.

The initial assessment was done when the patients received their newly fitted bespoke shoes with EVA inserts. The second assessment was at their next appointment in the Diabetic Foot Clinic.

Neuropathy assessment

The presence of nerve damage was assessed in both lower limbs by clinical examination of the ankle reflexes and foot pulses, together with recording of the vibration perception threshold (VPT).

Thermal sensory thresholds (TPT) were also recorded with a Thermal tester (Somedic, Stockholm, Sweden) from the dorsum of the foot and the response to five warm and five cold stimuli delivered at random time intervals was recorded. Clinical and neuropathy details in Table 6.5

6.3.4 Statistical analysis

Mean and SEM were calculated using the statistical analysis Statwork package. Comparisons between different types of shoes were made using the paired t-test and Wilcoxon test for a non-parametric distribution, in order to calculate the significance between groups.

6.4 Results

Comparisons were made in four groups of circumstances:

1.in prescription shoes versus patients' own shoes

2. in standard trainers versus patients' own shoes

3. in prescription shoes versus standard trainers.

4. in newly fitted versus worn-in prescription shoes with EVA inserts, at follow-up.

6.4.1 Comparison between peak pressures in prescription shoes and patients' own shoes (Table 6.2 and Fig. 6.1)

The peak plantar pressures (Fig. 6.1.1) measured in High Street shoes which had predominantly leather soles (437.8 ± 148.5kPa) were much higher than those in prescription shoes newly fitted with EVA inserts (286.4 ± 76.3kPa). This significant difference ($p<0.01$) was equivalent to a reduction in pressure with EVA inserts of 26.5 ± 4.9% (Fig. 6.2). From the individual graphs (Fig. 6.1.1) it was noticed that the percentage fall was the greatest in the two patients with the highest plantar pressures.

When patients were tested in their own trainers (187.4 ± 43.1kPa) and compared to prescription shoes (156.0 ± 31.3kPa), very little difference was detected (Fig. 6.1.2) and the small improvement (10.2 ± 18.5%) was not significant ($p=0.47$, NS) (Fig. 6.2). However the patients with the highest pressures did benefit again from prescription shoes (Fig. 6.1.2).

Plantar pressures actually increased significantly (Fig. 6.2) with 21.5 ± 9.2% ($p<0.05$) when patients were given new prescription shoes (210.7 ± 35.1kPa) compared to used prescription shoes (167.4 ± 28.3kPa). (Fig. 6.1.3).

6.4.2 Comparison between peak pressures in standard trainers versus patients' own shoes (Table 6.3 and Fig. 6.3)

The effect of trainers varied accordingly to the type of shoes the patient was already wearing (Fig. 6.4).

When compared to leather sole High Street shoes (489.2 ± 108.4kPa) the standard trainers (397.8 ± 110.2kPa) were a clear advantage (Fig. 6.3.1), reducing the plantar pressures by 19.2 ± 8.0% ($p<0.05$) (Fig. 6.4.1).

However when compared to used and worn prescription shoes (149.0 ± 37.0kPa), the new standard trainers (205.4 ± 40.9kPa) actually proved worse (Fig. 6.3.3), showing a trend to increase the pressures with 25.7 ± 14.0% ($p = 0.07$, NS). (Fig. 6.4.3).

New standard trainers (217.2 ± 40.7kPa) and used patients' own trainers (214.6± 37.0kPa) showed no statistical difference (3.3 ± 6.6% $p = 0.45$, NS) in the plantar pressures (Fig. 6.4.2)

6.4.3 Comparison between peak pressures in new prescription shoes and standard trainers (Table 6.4 and Fig. 6.5)

The effect of prescription shoes varied accordingly to the type of inserts the shoes were fitted with (Fig. 6.6).

In prescription shoes newly fitted with EVA inserts (228.4 ± 40.9kPa) the peak plantar pressures proved to be lower (Fig. 6.5.1) than those in standard trainers (376.4 ± 77.2kPa). This significant difference ($p<0.001$) was equivalent to a reduction in pressure with EVA inserts of 32.1±4.3%. (Fig. 6.6.1) .

However when compared to standard trainers (171.2 ± 15.7kPa), the new prescription shoes fitted with Poron inserts (199.0 ± 30.2kPa) had higher pressures (Fig. 6.5.2) showing a trend, although small and not statistically significant (10.5 ± 8.8%, $p = 0.14$, NS) to increase the pressures (Fig. 6.6.2).

Table 6.2. Peak pressures in prescription shoes versus patient's own shoes						
Patient	Sex	Type of own shoes	Plantar pressures in own shoes (kPa)	Type of bespoke shoes	.Plantar pressures in bespoke shoes (kPa)	Reduction in plantar pressures (%)
1. G.P.	F	Reebok boots	117	EVA	65	44
2. C.W.	M	Leather sole shoe (Jones)+ ski boot stiffner	153.6	EVA	114.3	25
3. P.L.	M	Leather sole shoe (Jones)	224	EVA	154	31
4. R.G.	M	Adidas trainers	298	EVA	135	54.6
5. J.F.	M	Leather sole shoe (Clarks)	175	EVA	136	22.2
6. E.G.	M	Trainers	597	EVA	226	62.1
7. W.J.	M	Leather sole shoe	246	EVA	161	34
8. R.W.	M	Trainers	790	EVA	223	71.7
9. P.G.	M	Trainers	269	EVA	228	15.2
10. J.G.	M	Worn out bespoke shoes	205	EVA	159	22.4
11. C.M.	F	Leather sole shoes (Freemans)	1137	EVA	600	47.2
12. I.T.	M	Rubber sole industrial shoe (Procter)	855	EVA	541 (first fit) 304 (second fit)	36.7 62.4
13. S.T.	M	Dr. Martens boots	207	EVA	177	14.4

Fig. 6.1 Comparison between peak pressures in prescription shoes and patient's own shoes

Fig. 6.1.1

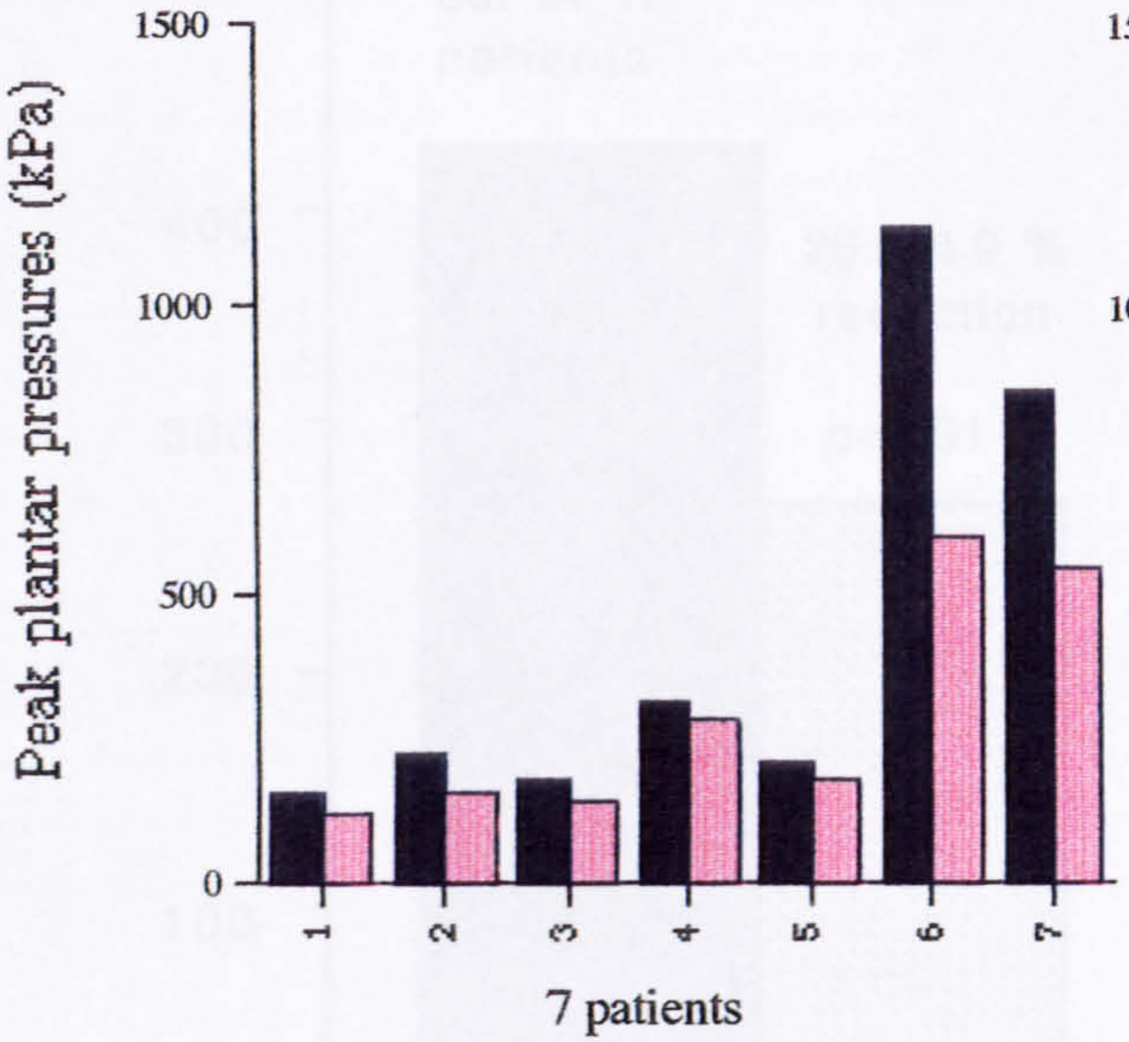


Fig. 6.1.2

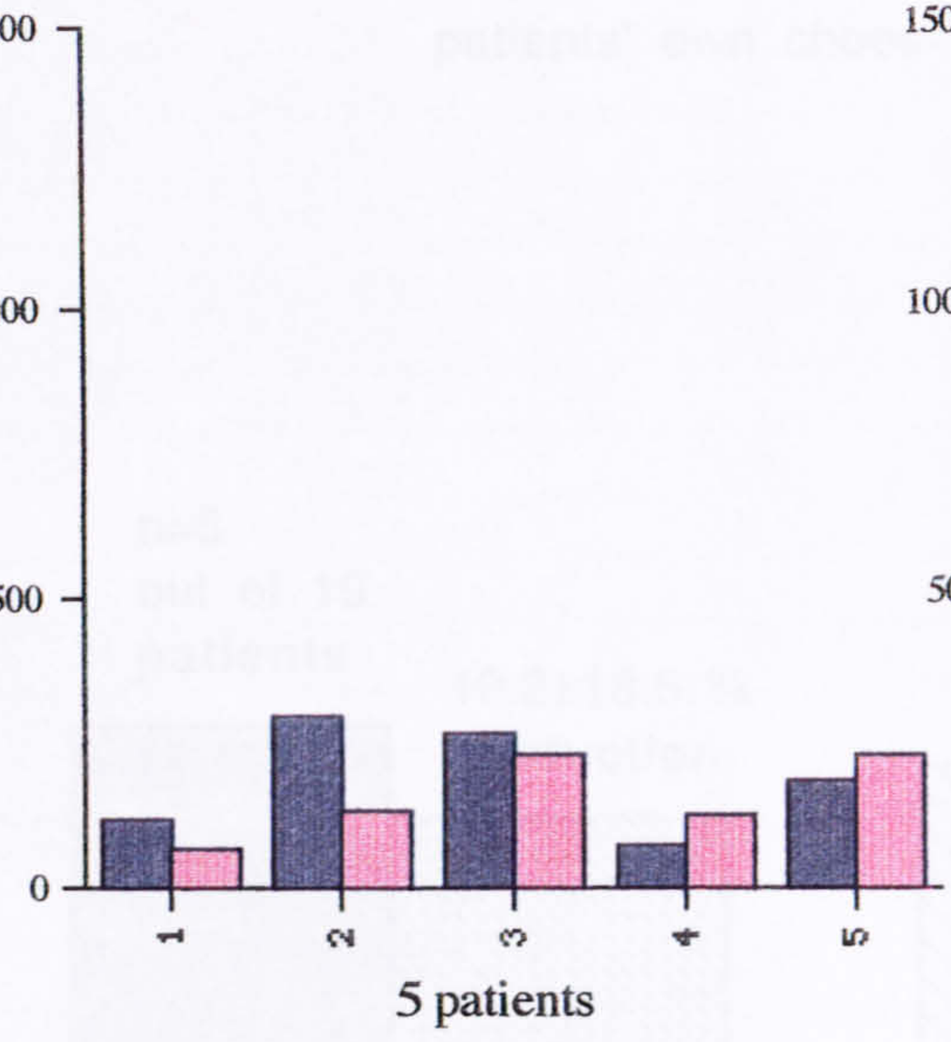


Fig. 6.1.3

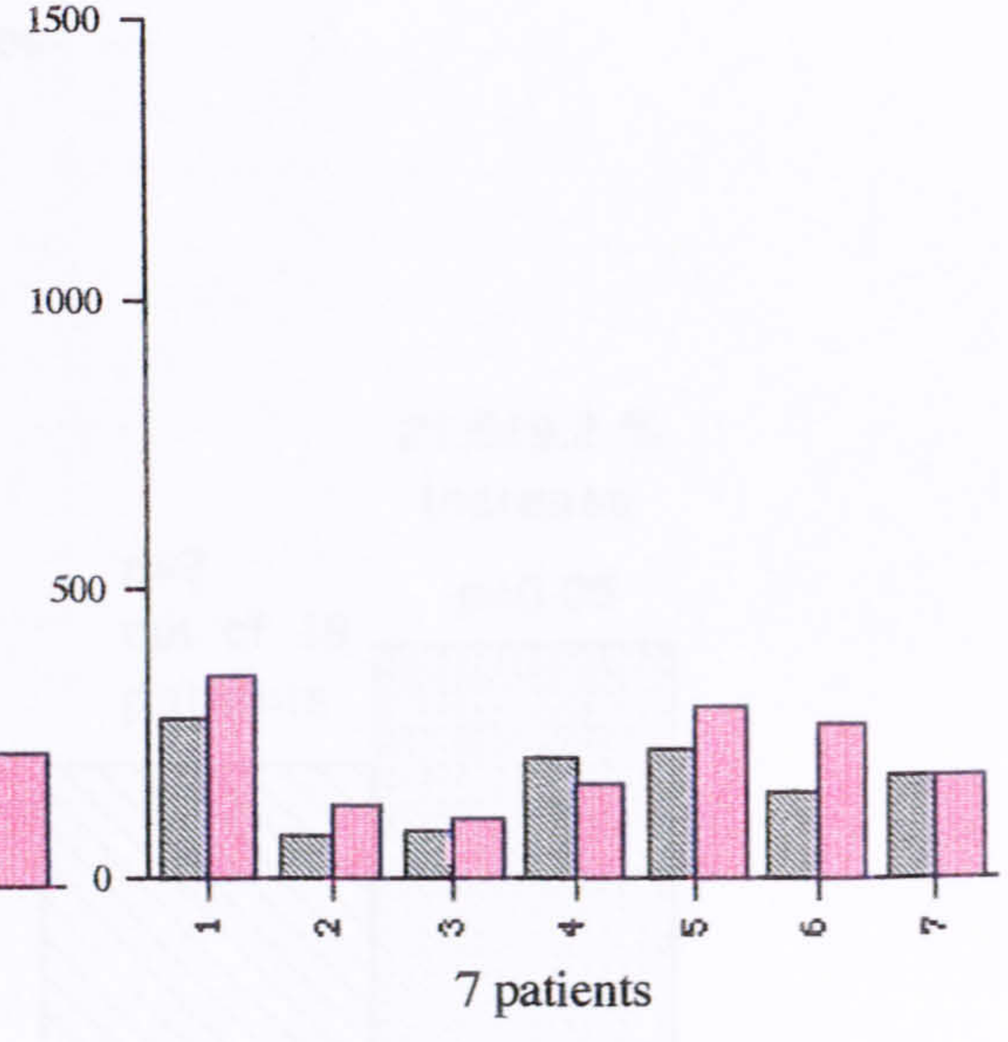


Fig. 6.2

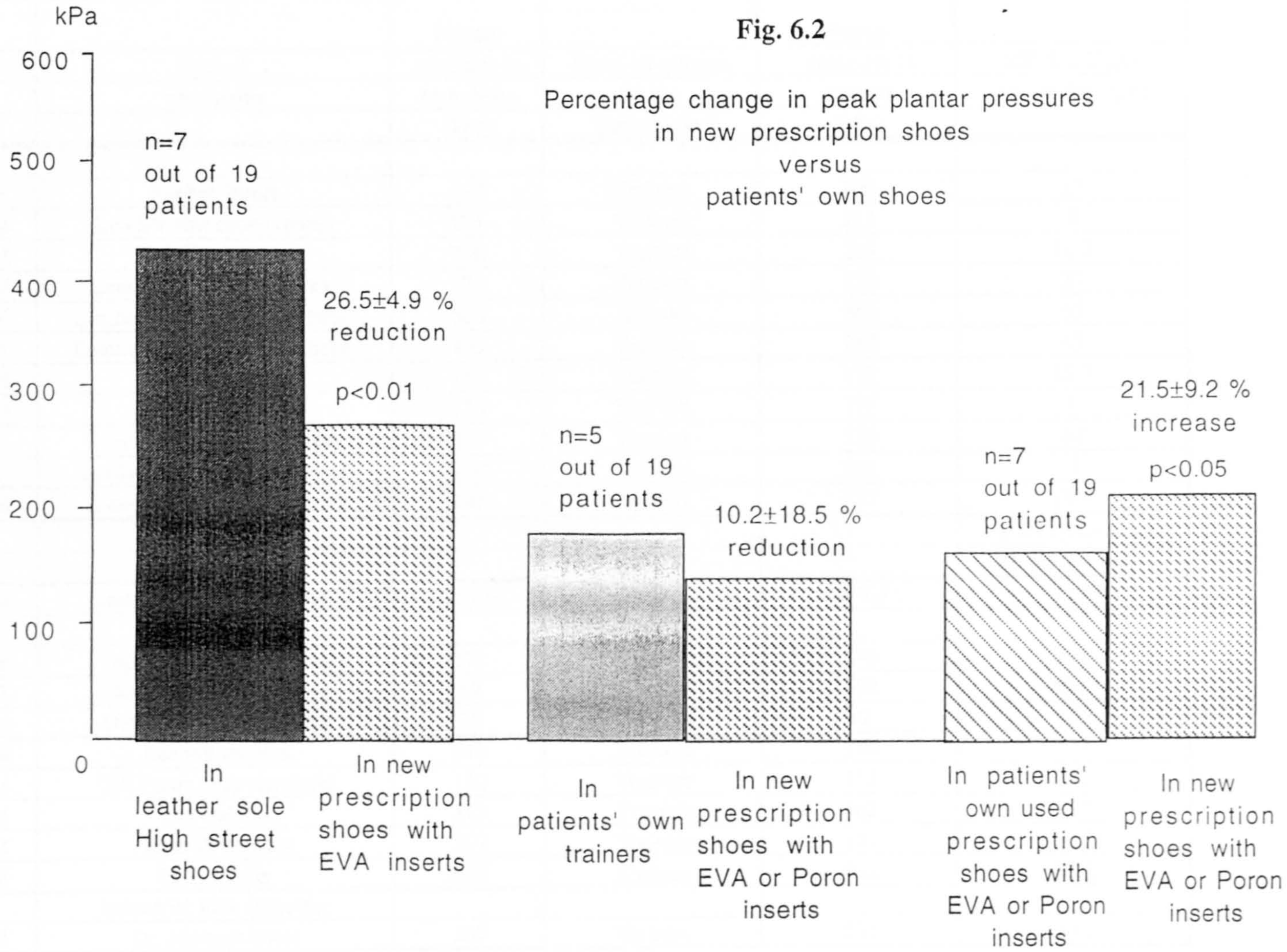
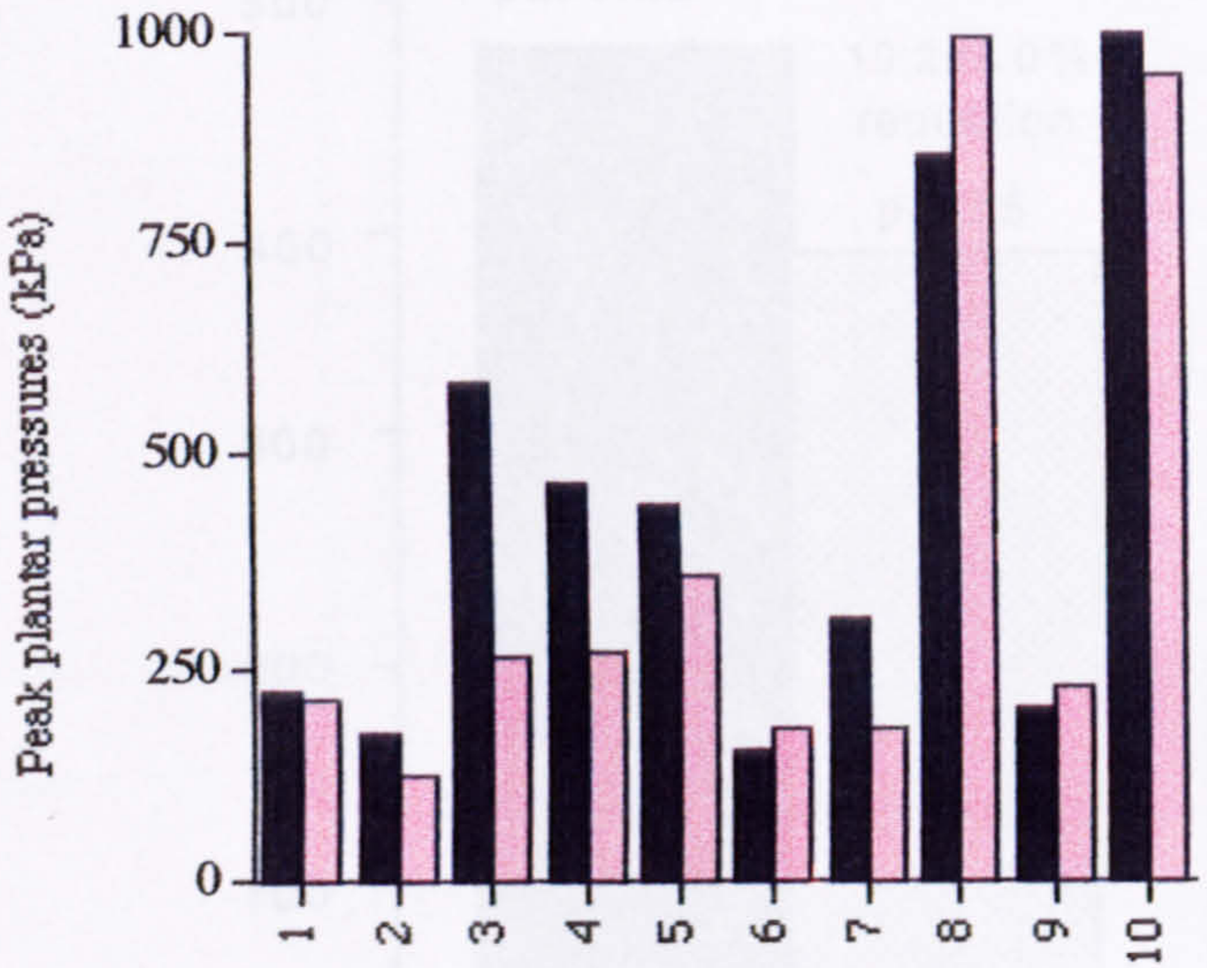

Percentage change in peak plantar pressures
in new prescription shoes
versus
patients' own shoes
kPa
600
500
400
300
200
100
0
n=7
out of 19
patients
26.5±4.9 %
reduction
p<0.01
n=5
out of 19
patients
10.2±18.5 %
reduction
n=7
out of 19
patients
21.5±9.2 %
increase
p<0.05
In
leather sole
High street
shoes
In new
prescription
shoes with
EVA inserts
In
patients' own
trainers
In new
prescription
shoes with
EVA or Poron
inserts
In patients'
own used
prescription
shoes with
EVA or Poron
inserts
In new
prescription
shoes with
EVA or Poron
inserts

Table 6.3 Peak pressures in standard trainers versus patient's own shoes

Patient	Sex	Type of own shoes	Plantar pressures in own shoes (kPa)	Standard trainers Clarks "Swing Low"	Plantar pressures in trainers (kPa)	% REDUCTION in plantar pressures
1. G.P.	F	Reebok boots	117	Trainers	100	27
2. P.L.	M	Leather sole shoe (Jones)	224	Trainers	213	5
3. R.G.	M	Adidas trainers	298	Trainers	263	11.7
4. J.F.	M	Leather sole shoe (Clarks)	175	Trainers	128	27
5. M.F.	F	Leather court shoe±high heels	586	Trainers	264	55
6. F.N.	F	Leather court shoe±high heels	469	Trainers	268	43
7. J.S.	M	Trainers	181	Trainers	158	12.7
8. J.H.	M	Old Poron insole	179	Trainers	178	1
9. G.J.	M	Leather sole shoe (Clarks)	307	Trainers	180	41
10. C.M.	F	Leather sole shoe (Freemans)	1137	Trainers	948	7
11. F.B.	M	Leather sole shoe (Epsom)	443	Trainers	357	19.4
						% INCREASE in plantar pressures
12. C.W.	M	Leather sole shoe (Jones)+ ski boot stiffner	153.6	Trainers	179.3	12.8
13. A.L.	M	Old EVA bespoke shoes	271	Trainers	346	21.6
14. E.P.	F	Old EVA bespoke shoes	69	Trainers	198	65.1
15. J.C.	M	Old EVA bespoke boots	76	Trainers	92	17.3
16. C.B.	M	Reebok trainers	110	Trainers	118	6.7
17. K.B.	M	Old Poron bespoke shoes	150	Trainers	212	29.2
18. W.J.	M	Old trainers	313	Trainers	362	13.5
19. P.G.	M	Reebok trainers	269	Trainers	303	11.2
20. I.T.	M	Rubber sole industrial shoe (Procter)	855	Trainers	992	13.8
21. S.T.	M	Dr. Martens boots	207	Trainers	231	10.3

Fig. 6.3 Comparison between peak pressures in standard trainers and patients' own shoes

Fig. 6.3.1

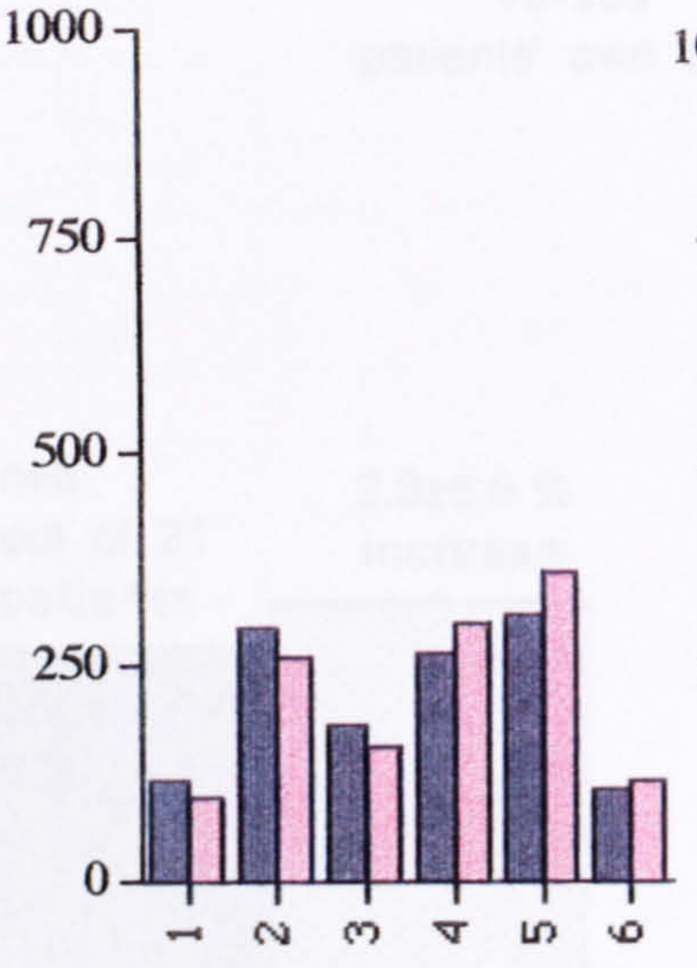


10 patients

Patients' own leather sole High Street shoes

Standard trainers

Fig. 6.3.2

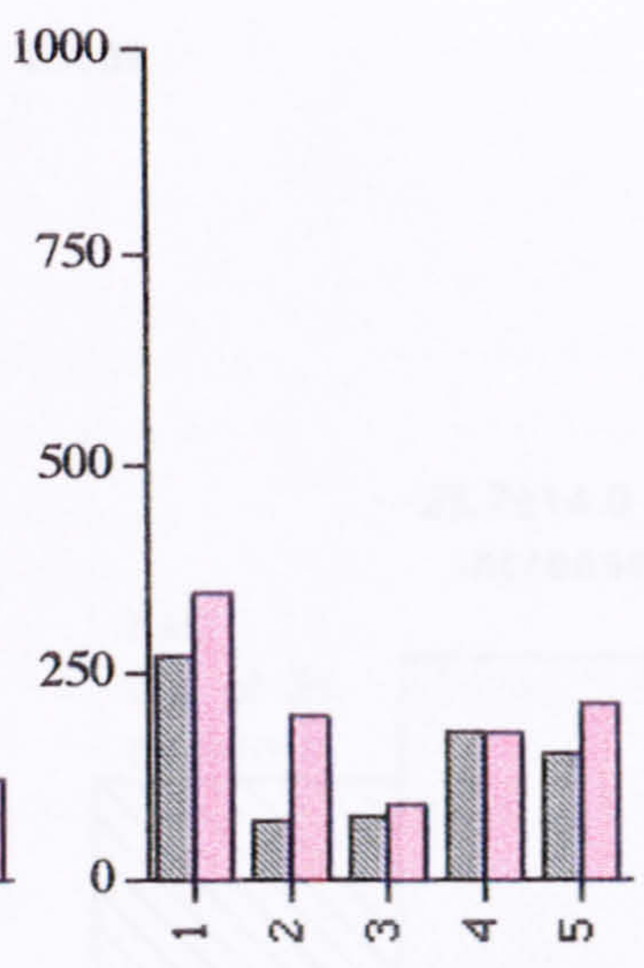


\+ + 6 patients

Patients' own trainers

Standard trainers

Fig. 6.3.3



\+ 5 patients

Patients' own used prescription shoes with EVA or Poron inserts

Standard trainers

Fig. 6.4

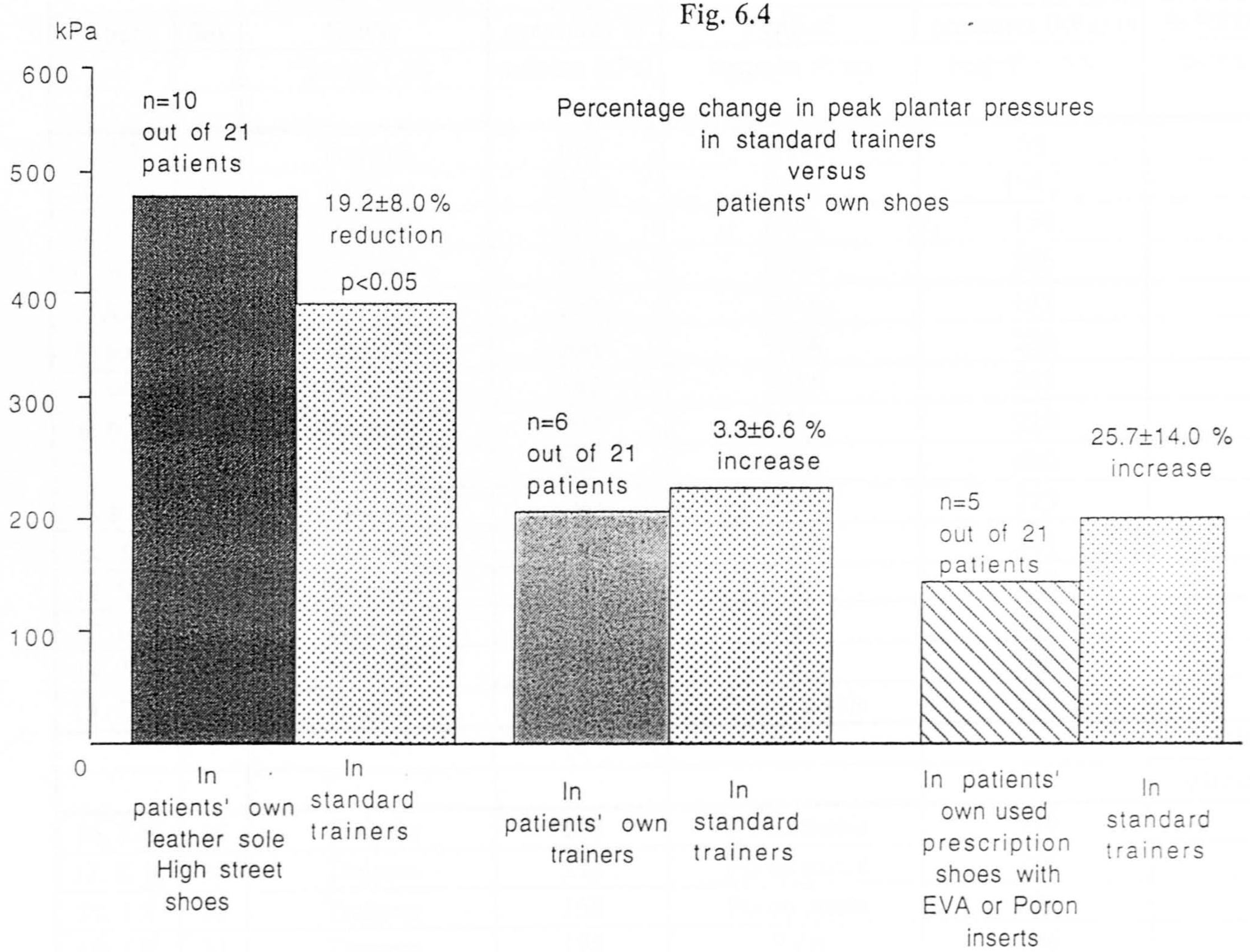
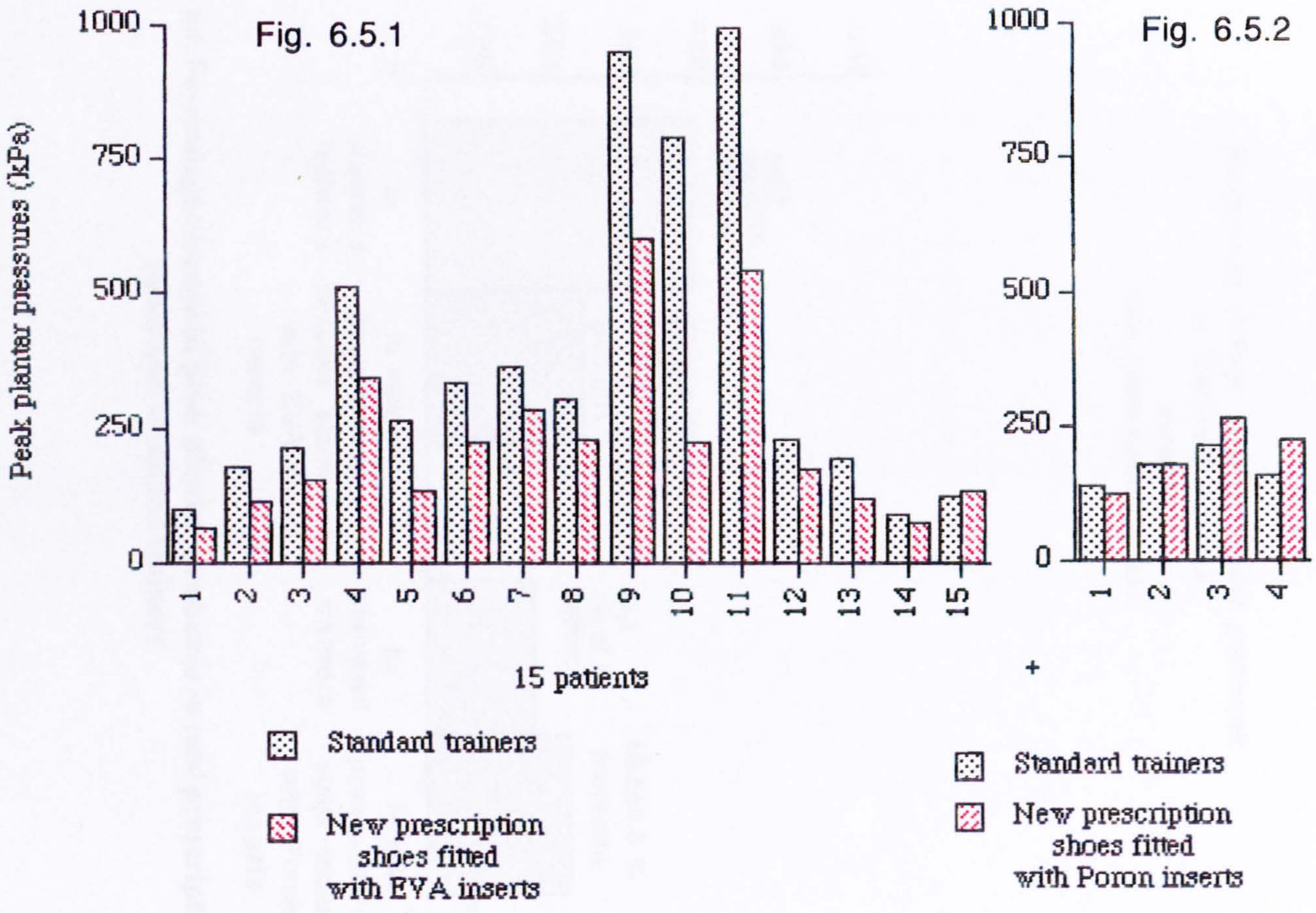

Percentage change in peak plantar pressures
in standard trainers
versus
patients' own shoes
kPa
600
500
400
300
200
100
0
n=10
out of 21
patients
19.2±8.0%
reduction
p<0.05
n=6
out of 21
patients
3.3±6.6 %
increase
n=5
out of 21
patients
25.7±14.0 %
increase
In patients' own leather sole High street shoes
In standard trainers
In patients' own trainers
In standard trainers
In patients' own used prescription shoes with EVA or Poron inserts
In standard trainers

Table 6.4 Peak pressures in prescription shoes versus standard trainers

Patient	Sex	Standard trainers Clarks ' Swing Low '	Plantar pressures in trainers (kPa)	Type of bespoke shoes	Plantar pressures (kPa) in bespoke shoes	% REDUCTION in plantar pressures
1. G.P.	F	Trainers	100	EVA	65	35
2. C.W.	M	Trainers	179.3	EVA	114.3	36.3
3. P.L.	M	Trainers	213	EVA	154	27
4. A.L.	M	Trainers	514	EVA	346	32
5. R.G.	M	Trainers	263	EVA	135	48
6. E.G.	M	Trainers	334	EVA	226	32
7. W.J.	M	Trainers	362	EVA	283	21.8
8. P.G.	M	Trainers	303	EVA	228	24
9. C.M.	F	Trainers	948	EVA	600	36
10. R.W.	M	Trainers	790	EVA	223	71.7
11. I.T.	M	Trainers	992	EVA	541	45.4
12. S.T.	M	Trainers	231	EVA	177	23.3
13. E.P.	F	Trainers	198	EVA	123	37.8
14. J.C.	M	Trainers	92	EVA	76	17.4
15. C.B.	M	Trainers	138	Poron insole	126	8.6
						% INCREASE in plantar pressures
16. J.H.	M	Trainers	177	Poron insole	178	0.5
17. K.B.	M	Trainers	212	Poron insole	266	20.3
18. J.S.	M	Trainers	158	Poron insole	226	30
19. J.F.	M	Trainers	128	EVA	136	5.8

Fig. 6.5 Comparison between peak pressures in new prescription shoes and standard trainers



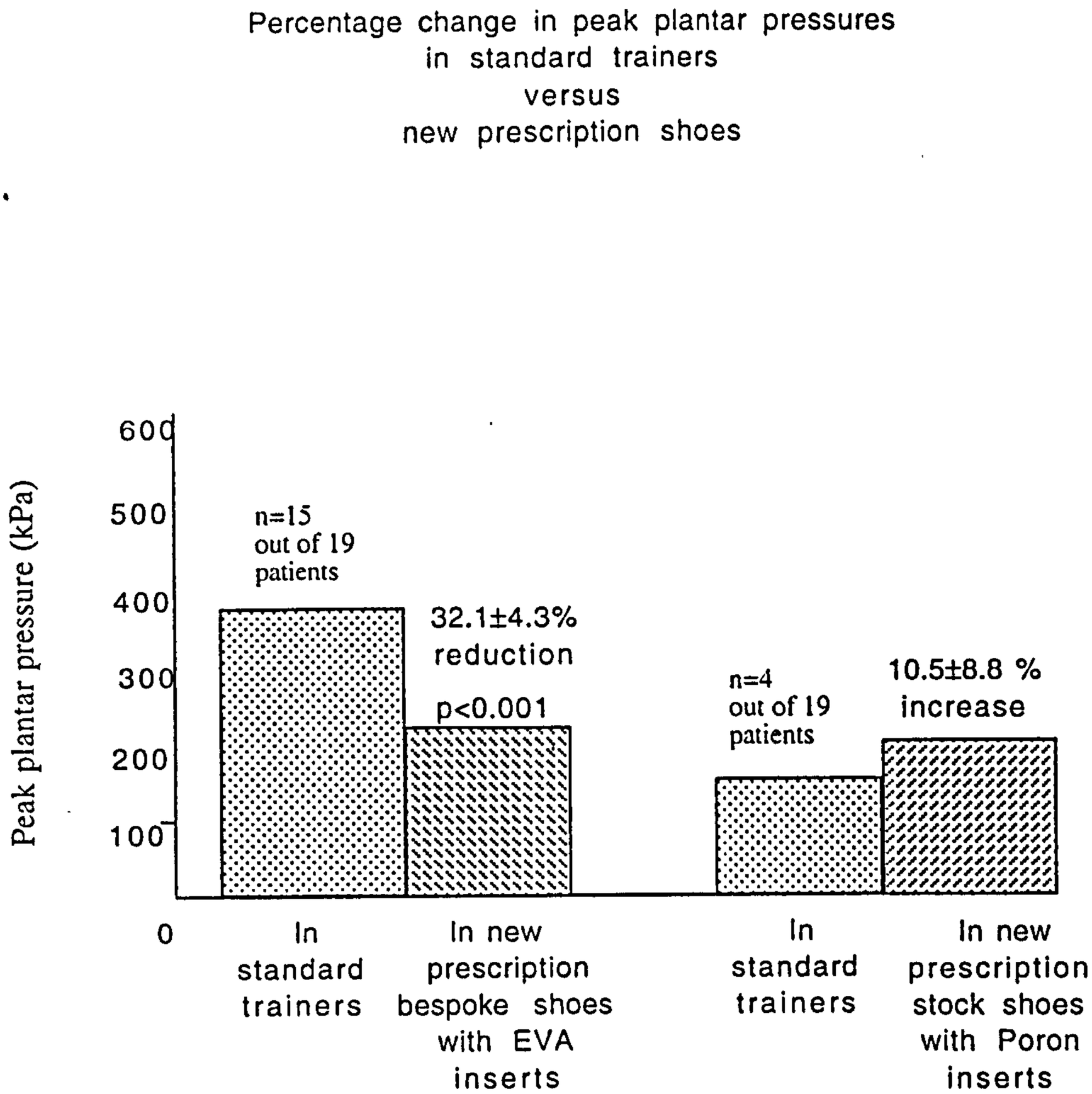


Fig. 6.6 Percentage change in peak plantar pressures in new prescription shoes and standard trainers

Table 6.5 Peak pressures in newly fitted and worn-in prescription shoes with EVA inserts at follow-up

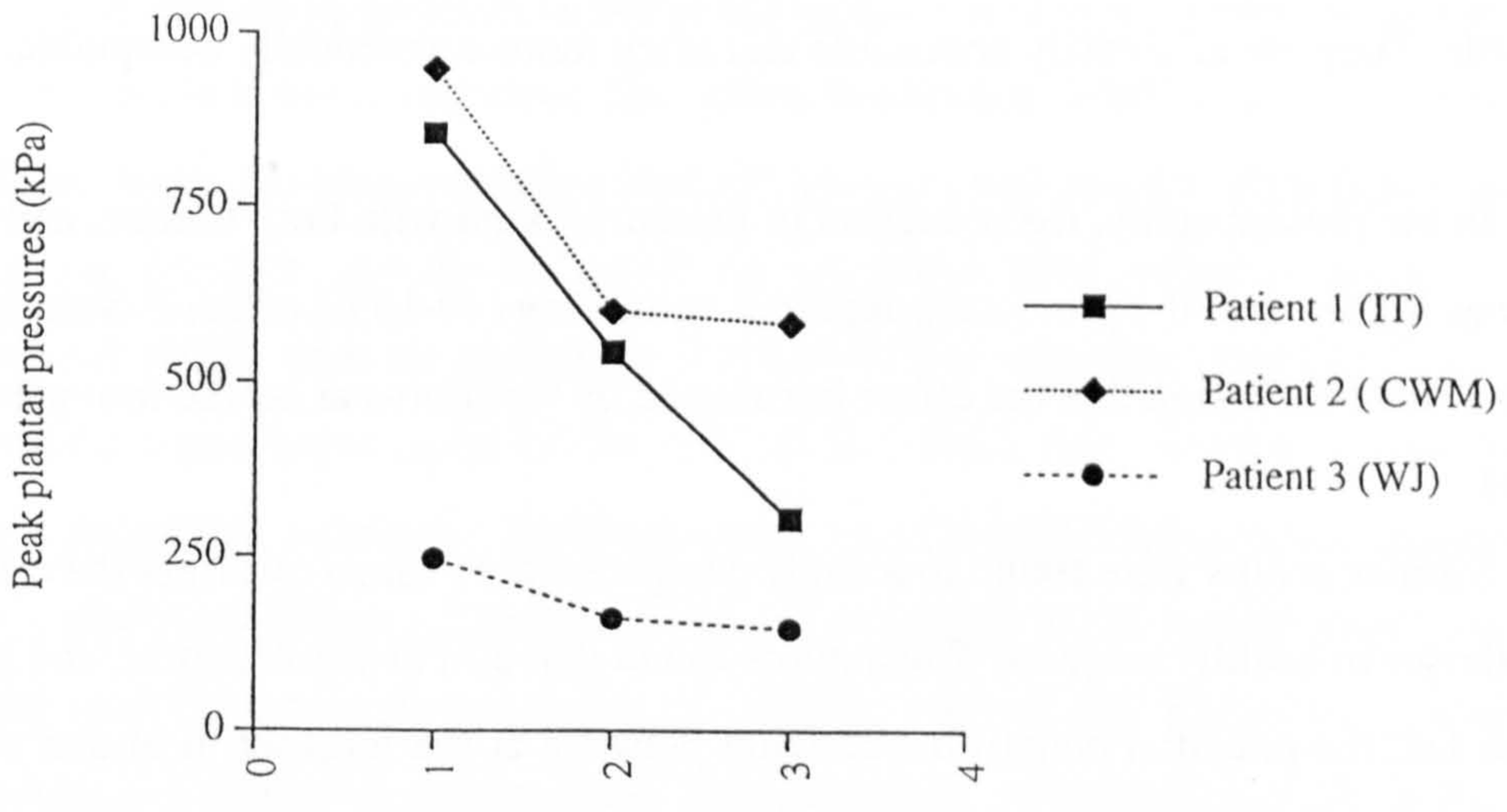
Patient	VPT (V)	TPT+ (C)	TPT- (C)	Peak pressures in new prescription shoes with EVA inserts at initial visit (kPa)	Peak pressures in new prescription shoes with EVA inserts at follow-up (kPa)	Change in peak pressures %	Peak pressures in standard trainers at initial visit (kPa)	Peak pressures in standard trainers at follow-up (kPa)	CV % Coefficient of variation of pressure measurements	Time interval (weeks)
I.T.	22	8.8	9.5	541 .	304	43.8	992	810	18.3	4
C.W.M.	31	2.1	3.4	600	582	3	948	902	4.8	6
W.J.	30	7.8	2.1	161	146	9.3	246	298	17.4	5

VPT= vibration perception threshold
TPT + = temperature perception threshold for hot
TPT - = temperature perception threshold for cold

6.4.4 Comparison between peak pressures in newly fitted and worn-in prescription shoes with EVA inserts at follow-up

The plantar pressures in EVA inserts showed a trend to decrease in time, from the first to the second visit to the Diabetic Foot Clinic which was at a mean interval of 5 ± 0.5 weeks (Table 6.5). The coefficient of variation of the repeated measurements was 13.5 ± 4.1% and it was calculated in standard trainers.

Fig. 6.7
Comparison between peak pressures in newly fitted and worn-in prescription shoes with EVA inserts at follow-up



In 3 patients the initial peak pressures in newly fitted bespoke shoes with EVA inserts (434.0 ± 137.5kPa) were higher than those measured (344.0 ± 127.4kPa) when the patients attended their next appointment to the Diabetic Foot Clinic. This equalled a further reduction in pressure of 18.7 ± 12.6% at the second visit (Fig. 6.7).

One patient (I.T.) demonstrated a considerable reduction (43.3%) in peak pressures at the second visit, after he had worn the bespoke shoes every day. Whereas the other 2 patients showed a trend to decreasing the pressures with 3.0% and 9.3%, which were within the limits of the coefficient of variation.

6.5 Discussion

This study has suggested that made-to-measure prescription shoes fitted with EVA inserts, although expensive, are the most efficient in reducing high plantar pressures developed in the neuropathic foot with a history of ulceration. EVA inserts in bespoke shoes proved to be better than leather sole High Street shoes and also better than trainers.

Although trainers were found to induce a smaller reduction in pressure than bespoke shoes with EVA inserts, trainers can provide a useful alternative to leather sole High Street shoes. Furthermore trainers proved to have a comparable effect, if not an benefit over prescription shoes fitted with Poron inserts. Trainers also have the advantage of being less expensive than the prescription shoes and therefore more affordable. They are also easily accessible and often more cosmetically acceptable.

In the present study, the reduction in pressure found with both trainers and fitted shoes was higher than the previously reported variability (10-15%) of the F-Scan insole, leading to the conclusion that the effect introduced by the footwear on the foot pressures was real.

Similar results were found in a study using also the F-Scan to assess the effect of foot orthoses in healthy subjects. The authors found that all Plastazote, cork, and plastic orthoses had the potential benefit of relieving pressure at the forefoot, heel and second to fifth metatarsal regions, but with a potential pressure increase in the midfoot area **(Brown, 1996).**

The prescription shoes newly fitted with EVA inserts significantly reduced by 26.5±4.9% the peak plantar pressures found in High Street shoes, which had predominantly leather soles. The leather sole High Street shoe group included a rubber sole shoe, knowing that there is no difference in plantar pressure between leather or rubber sole shoes as shown by **Nyska et al. (1995),** who found that the recordings for both leather and rubber sole shoes were almost identical in a study of shear and vertical forces. Furthermore when they tested a rocker bottom shoe, they found an important decrease (31-71%) in the longitudinal shear, whereas the vertical force was reduced by 26% but only under the second and third metatarsal heads, in those asymptomatic subjects. These results might be explained by findings of Sarnow et al. **(1994)** showing

that the shoes of the control group provided a lower pressure reduction than did those of diabetic patients. Furthermore our findings have shown that the greatest percentage fall was detected in the patients with the highest plantar pressures, suggesting that they would benefit the most from prescription footwear. As high plantar pressures are recognised to be an important ethiological factor in foot ulcer formation **(Veves et al., 1992)** it may be of benefit to set up a screening programme for high foot pressures in the diabetic population. Thus in order to prevent ulceration, prescription footwear would be recommended for those diabetic patients detected to have high foot pressures, even in the absence of a history of ulceration.

The reduction in pressure in prescription shoes was in agreement with a study in insensitive feet in Hansen's disease. The author **(Coleman, 1985)** studied 15 subjects in six different types of shoes using four discrete pressure transducers. Significant pressure relief in the forefoot was found in all the modified shoes when compared to the conventional shoes, with no change in pressure at the heel area. Another study using four discrete transducers taped to the sole of the foot, also showed a reduction in pressures measured under the forefoot when experimental shoes were compared to Oxford conventional shoes. The best results were obtained with extra depth shoes: a reduction of 31% was reported under the hallux, whereas all the other experimental shoes produced a smaller reduction in foot pressures, predominantly under the third metatarsal head **(Schaff and Cavanagh, 1990).**

In contrast a F-Scan study found the plantar pressures to be raised by 5% in extra-depth shoes when compared to patient's own shoes, however the inserts used in those extra-depth shoes were standard manufactured and not moulded **(Albert and Christiansen, 1994)** These findings stress the fact that although extra-depth shoes provide accommodation of deformity, they need to be fitted with a moulded insert to reduce the foot pressures per se. In a further study Corbett et al. **(1993)** highlighted the importance of a custom-made orthotic device in decreasing the plantar pressures under the first metatarsophalangeal joint by 31%, which was comparable to the reduction introduced by a fibreglass short leg walking cast, frequently used in the treatment of active ulcers for its qualities in pressure relief.

Also in a similar study using the F-Scan to assess the plantar pressures in the pronated diabetic foot, a reduction of 30-40% in pressure was found in extra-depth shoes fitted with custom-made orthotic inserts. A concomitant increase (5-10%) in total contact area between the foot and shoe during gait **(Albert and Rinoie, 1994)** was also described suggesting that the custom-made orthotics can reduce the risk of ulceration by redistributing the pressures on the plantar surface.

When patients were tested in prescription shoes and compared to their own trainers, very little difference was detected and the small improvement (10.2 ± 18.5%) was not significant. This might be due to the fact that although EVA inserts reduced pressures in 3 patients, the Poron inserts worn by another two patients in their prescription stock shoes actually increased the pressures. These observations may highlight the benefit of moulded inserts, such as those found in good quality trainers, over flat inserts, such as those found in stock prescription shoes with Poron insert. However further controlled studies with a larger number of patients are required to solve this question.

In a similar study, Schaff and Cavanagh **(1990)** examined the effect on plantar pressures of a conventional extra-depth shoe versus an extra-depth shoe modified into a "rocker bottom " configuration with a 24° rocker. They found that the peak pressures in the rocker shoe were reduced with approximately 30% in the forefoot (medial and central) with an increase in pressure in the heel, midfoot and lateral sides of the forefoot. These findings emphasis the influence of a correctly designed shoe on its ability to reduce pressure in the areas at risk diffusing it towards other areas of lower pressure.

However it is important that this shift does not increase the pressures over the threshold for risk of ulceration in another area. Therefore the moulded inserts as found in trainers might be preferable to the flat ones as Poron inserts. Similarly individually designed moulded inserts as EVA inserts might be preferable to standard manufactured stock moulded inserts as found usually in trainers. In some cases of severely deformed feet with a history of ulceration the individually designed moulded inserts are a necessity, although they are expensive.

Although the findings of these previous studies compare well with the degree of pressure reduction in prescription shoes found in the present study, surprisingly we also found an increase in pressures. Newly fitted prescription shoes with EVA or Poron inserts showed higher pressures than used prescription shoes fitted with the same type of insert suggesting that the newly fitted inserts for prescription shoes have not yet reached their maximum potential in reducing foot pressures. The EVA polymer is a soft insert material easily mouldable and hence with good cushioning qualities (**McKenzie et al., 1985**) and there is the possibility that it continues the moulding process during wearing. However its disadvantage may arise from the risk of flattening and cessation of cushioning effect.

Nevertheless from these observations, it seems that the EVA inserts are able to maintain their ability to reduce pressure for a long time. The cushioning effect obtained in EVA inserts by layering materials with decreasing densities seems to be effective and preserved in time. Alternatively there is the possibility that the design of the insole by orthotists is not ideal and that the imperfections, which unfortunately are not always minimal, are corrected through the wearing-in process.

Likewise the used prescription shoes with Poron insert had lower pressures than the new ones. Although there is very little scientific literature, the Orthotic Department suggests that a possible moulding process can not be excluded in Poron inserts. The other possibility is that a change in the shape of the extra-depth stock prescription shoes fitted with Poron inserts, possibly related to wear-in of the shoes, would allow better accommodation of the foot deformity.

Nevertheless the increase in pressure found in our study, when changing from both used Poron and EVA to new Poron and EVA inserts leads to a conclusion with clinical implications: although patients have been stabilised in EVA or Poron inserts, it is important to note that when they change to a similar new insert it would be advisable to warn them to 'break in' the insert gradually.

Furthermore in the present study, an additional reduction (19%) in foot pressures was found at follow-up. This is demonstrated in the three patients who came for repeated measurements of their plantar pressures in prescription shoes with EVA inserts. The pressures had a trend to decrease from the initial visit when the patients received their newly fitted prescription shoes to the second visit a few weeks later, during which the patients were supposed to wear the shoes every day.

However the degree of further pressure reduction varied in each individual, being probably related to the level of activity and mobility of each patient and also to their compliance with the prescription shoes. Future longitudinal studies are needed to assess the compliance of our patients to the inserts. Previously it has only been shown in a single follow-up study **(Chantelau et al., 1990)** that therapeutic shoes with cushioned inserts for diabetic feet at risk decrease the morbidity by reducing the recurrent foot lesions from 87% in those who wore the shoes irregularly, to 42% in those who worn the shoes on a regular basis.

Nevertheless these observations of the present study, support the previous hypothesis that there is a continuation of the moulding process inside the shoe during wearing-in. EVA polymer being an easily adjustable material allows a better fit to the individual characteristics of the foot and continues the moulding process during wearing. The bespoke shoes with EVA inserts are an attempt to combine the use of a rigid sole with the necessary cushioning, therefore the apposition of layers with different densities. The most dense and rigid layer is placed at the base to support the insensitive foot with limited joint mobility, while layers of decreasing density were placed on top to insure the cushioning effect. Therefore the upper layers seem to continue the moulding process during wearing. Thus, in clinical practice, patients are usually advised to wear the newly fitted shoes for longer time intervals each day for this purpose.

Further longitudinal studies assessing the life-time of the EVA and Poron inserts are also needed in order to characterise the degradation rate of the material with use and its effect on in-shoe plantar pressures. A previous study assessing not the plantar pressures, but the shock absorption ability during one year of general use in Poron and Viscolas insoles has shown a deterioration in their performance after 6-9 months of use,

whereas Plastazote and Gait Aid insoles performed even more poorly **(Pratt, 1990)**. In another study which tested different inserts, it was demonstrated that a Plastazote insert which was worn for 72 hours produced the worst results in pressure relief **(Pratt et al., 1986)**, but it seems that there are no similar long term data for the effect of EVA inserts on plantar pressures.

The effect of trainers on plantar pressures varied accordingly to the type of shoes the patient was already wearing. When compared to leather sole High Street shoes the standard trainers were a clear advantage, reducing the plantar pressures by 19%, probably because trainers can provide more cushioning and more support on the midfoot area due to their soft moulded insert with a midsole arch. This is in agreement with a study by Perry et al., which measured plantar pressures in trainers compared to leather-soled Oxford-style shoes and to barefoot conditions. Their findings showed that inexpensive running shoes relieved the total load through pressure redistribution to the forefoot but also to the heel, although it is known that the neuropathic ulcers which occur under the heel are rarely due to gait. The greatest relief was obtained in the feet which had the highest pressures when they were unshod. The study concluded that patients with neuropathy should be discouraged from wearing leather-soled Oxford-style shoes because of the risk of ulceration due to increased foot pressures **(Perry et al., 1995)**.

However in our study there was no statistical difference in the plantar pressures measured in standard trainers versus patients' own trainers. Similar results were found in another study which ranked for comfort 4 different types of inserts in Adidas trainers and measured the in-shoe plantar pressures using an EMED system. It found that any type of insert which was perceived by subjects as being comfortable, had in fact a similar effect on peak plantar pressures: all the 'comfortable' inserts redistributed the pressures evenly on the plantar surface and lowered the pressures at the forefoot **(Chen et al., 1994)**.

In contrast, a trend to increased pressures in standard trainers was found when compared to used prescription shoes. As discussed previously, it seems that used prescription shoes tend to have lower pressures than the new ones because of a possible continuation of the moulding process. Therefore it is not surprising that the new

standard trainers which had not been worn extensively previously were less efficacious in reducing pressure than used prescription shoes which had been worn every day. Nevertheless these findings support Cavanagh's guidelines for prescription footwear **(Cavanagh, 1995)**, in which trainers are considered to be an acceptable choice only for those individuals who are free from deformity, but an advantageous alternative to leather sole High street shoes.

When compared to standard trainers the effect of prescription shoes varied accordingly to the type of inserts the shoes were fitted with. The prescription shoes newly fitted with EVA inserts significantly reduced by 32% the peak plantar pressures found in standard trainers. This may be explained by the fact that standard trainers containing a standard moulded insert made from a semi-rigid material had less cushioning effect than the soft moulded EVA insert of a prescription shoe which was made to fit the characteristics of an individual foot including its deformity. These findings are in agreement with another study of foot pressures measured in running shoes (trainers). Although the trainers decreased the pressures by about 30%, they showed higher pressure values than the normal street shoe when fitted with a soft insole **(Schaff et al., 1988)**.

In Schaff's study comparisons between different types of insoles were also made; the same shoe was fitted with a soft and a hard insole and then compared to barefoot conditions. A reduction of 25% was obtained with the soft insole in the diabetic group, whereas only a 17% reduction was obtained in the control group **(Schaff et al., 1988)**. They concluded that the forefoot pressures are influenced by the geometry of the sole and the type of insert material used. All these findings point to the fact that the insert effect on plantar pressures is highly dependent on the design and the type of material used in its manufacturing, which influences the redistribution of pressure and the cushioning effect.

As a reiteration of the previous statement a trend, although small (10.5%) and not statistically significant, to increase pressure was found in new prescription shoes fitted with Poron inserts when compared to standard trainers. The 'New Style' orthopaedic shoes with Poron inserts are conveniently prescribed because of their immediate availability to the patient, but our figures show that the new Poron insert is

often associated with an increase in pressures when substituted for patient's used Poron insert or even for good quality trainers with extra-cushioning such as standard trainers. The cushioned insert with a midsole arch found in our standard trainers was obviously more advantageous than the flat insert of the stock shoes with a Poron insert. This might be due to the fact that the Poron insert contains a very resilient material, which does not deform with time and has good shock absorption properties. However it is flat, not moulded, and because of its resilience, the moulding process and the cushioning effect are not significant. Furthermore the midsole in trainers is usually considered to have as a primary function, the reduction of in-shoe reaction forces or the redistribution of pressure over a larger area. These findings are in agreement with those of Lord and Hosein showing that the pressure was significantly reduced in moulded inserts when compared to flat inserts fitted into the same shoes **(Lord and Hosein, 1994)**.

Unfortunately the number of patients with Poron inserts who were taken into the study was too small to achieve statistical significance, but clinically the standard trainers seemed to be more efficient in relieving pressures than the stock prescription shoes fitted with a standard, not individually designed Poron insole, which might be more expensive than trainers.

This highlights the potential role which trainers may have in prevention of ulceration in the early stages of the foot at risk, when is not deformed and has good proprioceptive sensation. Trainers also provide an option which is more socially and cosmetically accepted by patients. At this stage the protection can be achieved without the expenses implied by individually designed inserts and bespoke shoes such as our prescription shoes with EVA inserts. They are nevertheless vital for patients with recurrent ulceration and feet at risk, who need an individualised choice of cushioning materials and insert design.

This study discusses both the principles and practice of prescribing therapeutic insoles and indicates that much greater attention should be paid to in-shoe dynamic pressure measurement. It would be advisable that shoes should be prescribed and fitted in centres which use this equipment to achieve the optimal outcome.

This study also indicates that in certain circumstances there is an increase in foot pressures in patients going from their own shoes to the trainers supplied or Poron

insoles. Therefore there is a need for immediate 'on the spot' pressure assessment of the effect of recommended footwear, particularly of stock orthopaedic shoes with Poron insoles in comparison with their own footwear. This stresses the importance of a Shoe Clinic within the Diabetic Foot Centre.

There have been no previous studies examining the value of certain High-Street shoes and this study has proven that sometimes trainers could be more efficient than certain types of supplied footwear. Therefore there is a need for systematic assessment of High Street shoes and their inserts. There is an array of shoes and inserts available to our patients and we know very little of their properties and their ability to redistribute pressure in diabetic patients. The methods described above allow investigations of the prescription footwear and High-Street shoes. This will help to improve the advice given to patients about shoes and footwear, which at present is by necessity lacking detail of information.

Despite the apparent success of the fitted shoes in relieving pressures, most of the studies were of a cross-over design. The necessity arises now for follow-up studies regarding the time-dependent characteristics of different types of footwear and their effect in time on the plantar pressures.

Conclusions and rationale for future studies

This study has shown that made-to-measure prescription shoes fitted with EVA inserts, although expensive, are the most efficient in reducing high plantar pressures developed in the neuropathic foot with a history of ulceration. EVA inserts in bespoke shoes proved to be better than leather sole High Street shoes and also better than trainers.

However when new and worn-in prescription shoes fitted with EVA inserts were compared, the latter showed even lower pressures than the new ones suggestive of a continuation of the moulding process with wearing.

Furthermore when new and used prescription shoes fitted were compared, the latter also showed lower pressures leading to the clinical recommendation that new prescription shoes should undergo a gradual 'break in' process.

The greatest percentage fall in prescription shoes was found in the patients with the highest plantar pressures, suggesting that they benefit the most from prescription footwear. As high plantar pressures are recognised to be an important aetiological factor in foot ulcer formation **(Veves et al., 1992)** it may be of benefit to set up a screening programme for high foot pressures in the diabetic population. Then in order to prevent ulceration, prescription footwear would be recommended for those diabetic patients detected to have high foot pressures, even in the absence of a history of ulceration.

Although trainers were found to induce a smaller reduction in pressure than bespoke shoes with EVA inserts, trainers can provide a useful alternative to leather sole High Street shoes.

Furthermore trainers proved to have a comparable effect, if not an benefit over prescription shoes fitted with Poron inserts. Trainers also have the advantage of being less expensive than the prescription shoes and therefore more affordable. They are also easily accessible and often more cosmetically acceptable

Finally, this study confirms the feasibility of quantitative assessment of foot pressure changes with different types of footwear on a cross-sectional basis. It also highlights the need for longitudinal studies to assess the characteristics and the life-time of the insoles and to correlate these with recurrence of ulceration.

The life-time of an insole is not known and longitudinal studies to define physical and clinical end-points are needed. They could be carried out with the F-Scan technology. The definition of the end-points has to be based on quantitative assessment of the ability of the insole to maintain the redistribution of pressure as well as its usefulness in preventing the recurrence of foot ulcer.

It is not known for how long an insole should be used. Whether replacement should depend on simple assessment of its physical characteristics or be related to more scientific pressure measurements to assess its capability to reduce peak pressures and maintain them at a safe level to prevent recurrence of ulceration remains to be studied.

These findings stress the usefulness of modern techniques, such as F-Scan, as a visual and quantitative aide in shoe design, as it was used in a similar study using an interactive computer graphics system for the design of moulded and orthopaedic shoe lasts **(Lord and Foulston, 1991; McAllister et al., 1991)**. These techniques should now be used to address the problems of design and manufacture of inserts and prescription shoes for the diabetic foot.

Chapter 7. MICROCIRCULATORY FACTORS AND THEIR ROLE IN THE PATHOGENESIS OF THE DIABETIC FOOT

The importance of the microvascular defects in the aetiology of foot ulceration among many other risk factors has not yet been fully investigated. Healthy tissues with a normal structure and function rely on intact microcirculation and on its roles of transportation and interchange of hormones and nutrients plus maintenance of tissue fluid homeostasis, clearance of waste products of metabolism and not least, tissue defence and repair (**Tooke et al., 1996**) are important in maintaining the viability of various tissues.

This last role of microcirculation can lead to a possibly simplistic, but fundamental concept which takes in consideration the role of the skin necrosis (which implies microvascular impairment) and the potential additional role for intrinsic microangiopathy of the foot tissues in the pathogenesis of the foot ulceration.

7.1 Pathophysiology of cutaneous diabetic microangiopathy

New techniques for the assessment of the microcirculation have been developed in recent years: plethysmography, capillaroscopy, laser Doppler flowmetry and iontophoresis (**Tooke, 1993**) facilitated the deduction of the 'haemodynamic hypothesis' of diabetic microangiopathy.

Clinical observation and estimates of blood flow formed the basis for this hypothesis suggesting that increased microvascular pressure and flow characterise early stages of diabetes. The microvascular endothelium responds to increased capillary pressure as an injury, with excessive production of extravascular matrix proteins resulting in microvascular sclerosis. In the arterioles, the sclerotic process is expressed as hyalinosis and in the capillaries, as basement membrane thickening, which is the ultrastructural hallmark of diabetic microangiopathy. This sclerosis continues in time and in long-term diabetes, a reduction in vasodilatation occurs with decreased maximal hyperaemia plus loss of autoregulation (**Tooke, 1986**).

Although this hypothesis takes into account the effect of diabetes per se on the microcirculation, IDDM and NIDDM may behave differently.

The effect of IDDM on microcirculation seems to be in accord with the characteristic stages of the "haemodynamic" theory: capillary pressure increased early in the course of IDDM, even in children who also demonstrated autoregulatory abnormalities (reduced posturally induced vasoconstriction) (**Rayman et al., 1986, Shore et al., 1994**), whereas long duration IDDM per se introduces a limitation of the maximum hyperaemia independent of recent blood glucose control (**Walmsley et al., 1990**). However the effect of NIDDM on microcirculation seems to be different from IDDM. Early on the course of the disease normal capillary pressure, but abnormal maximum hyperaemia were found. This may be related to long periods of hyperinsulinemia in response to increased insulin resistance **(Jaap et al., 1994)** characteristic for NIDDM pathogenesis.

In conclusion, diabetes whether IDDM or NIDDM, has a definite effect on the microvascular function inducing a microangiopathy which may play a role in the aetiology of the foot ulceration.

7.2 The role of microvascular function abnormalities in the pathogenesis of foot ulceration

Microangiopathy studies showed an early reduction in maximum hyperaemia in NIDDM which might provide an explanation for their increased risk of foot ulceration, present frequently at diagnosis of diabetes. The microcirculatory defects interact with neuropathy and macrovascular disease, as major risk factors involved in the foot ulceration.

Table 7.2.1 The microvascular haemodynamics in the diabetic foot

Physiological abnormality	**Consequences**
High resting flow particularly on dependency with loss of pressure autoregulation	Oedema Capillary compression Increased diffusion distances Extrinsic pressure from footwear
Impaired peak hyperaemia when tissue demands are increased	Impaired healing and inability to counteract infection

Abnormal pressures were found in the toes of diabetic neuropathic patients with a history of ulceration when compared to non-ulcerated neuropathic patients highlighting the contribution of distal ischaemia of digital arteries in the pathogenesis of foot ulceration (**Stevens et al., 1993**).

An impaired blood flow autoregulation concomitantly with increased blood flow in the foot leads to oedema formation, visible in neuropathic patients without any deficiency in their kidney function. Neuropathic oedema is more likely seen in patients presenting with foot ulceration probably because it induces a simple mechanical effect with increase in the extrinsic pressure from their footwear. Also the oedema may increases the intracapillary diffusion distances disturbing the nutritive blood flow.

Another possibility might be that capillaries are compressed by the high pressure of the interstitial fluid, with subsequent functional failure compromising the nutrition of the adjacent tissues and increased risk of localised tissue necrosis. This hypothesis seem to be supported by recent studies of magnetic resonance imaging in diabetic patients with a history of foot ulceration, which found 'drop outs' on the image of the foot. These are thought to represent accumulation of haemoglobin degradation products. The presence of such soft tissue haemorrhages might be a result of increased pressure load or shear forces, although the vertical pressures were not different in patients with or without these soft tissue haemorrhages (**Brash et al., 1995**). These findings may be related to the presence of membranocystic lesions found similarly in skin biopsies taken from the shin and feet of diabetic patients, which showed microangiopathy changes in the small vessels of the dermis and subcutaneous tissue (**Sueki et al., 1986**) Likewise they might reflect intrinsic capillary fragility which is associated with risk of microangiopathy, highlighting once more the role of microcirculation defects in the aetiology of foot ulceration.

Furthermore the diminished hyperaemic response to noxious stimuli due to a reduced axon reflex in neuropathy is likely to delay healing of lesions precipitated by minor or major trauma easily unnoticed by an insensitive foot due to neuropathy.

In conclusion, abnormal arteriolar pressures, impaired blood flow autoregulation concomitantly with increased blood flow leading to oedema formation and diminished hyperaemic response to noxious stimuli are important in the pathogenesis of foot ulceration.

7.3 Neuropathy and microvascular function in the diabetic foot

The diabetic foot ulcer is the extreme manifestation of the failure of the microcirculatory function and peripheral nervous system, which are closely related. Diabetic peripheral neuropathy affects the small nerve fibres early in its course: unmyelinated sensory C fibres, myelinated A delta fibres (transmitting pain and temperature sensation) and sympathetic fibres (**Said et al., 1983; Guy et al., 1985**) which control the autoregulation of skin microvasculature are, thus damaged early.

The skin microcirculation of the foot consists of nutritive capillaries and arterio-venous shunts (predominantly on the pulp of the toes) with a role in thermoregulation. In patients with peripheral neuropathy an increased blood flow was found in measurements of total forefoot blood flow using venous occlusion plethysmography similar to the changes seen after sympathectomy (**Watkins 1983**; **Edmonds et al, 1982; Boulton, 1982**), which results in arterio-venous shunting by-passing the capillary nutritive circulation. Studies of TcO2 in the foot, Doppler sonograms, measurements of foot venous pressure and microsphere partioning studies have shown evidence of arterio-venous shunting (**Tooke and Brash, 1996**): however the 'steal ' effect from the capillary circulation by arterio-venous shunts has not been demonstrated in neuropathy: nailfold capillary flow velocity was found to be also increased, although that might be a consequence of higher skin temperature due to the increase in the arterio-venous shunt flow (**Flynn et al., 1988**). It remains to be determined whether the increased capillary flow has the ability to respond to raised tissue demands secondary to the increase in the skin temperature and whether the capacity to vasodilate is preserved.

The effects of diabetic neuropathy on the microcirculation were assessed by measuring the posturally induced vasoconstriction which depends on an intact peripheral nervous system. In non-diabetic controls when the foot is lowered below heart level, both capillary and arteriovenous shunt flow are reduced (**Hassan et al., 1988**) to avoid an increase in the hydrostatic pressure on dependency in the microcirculation and oedema formation (**Flynn et al., 1989**). The postural vasoconstriction has been found to be reduced in patients with neuropathy (**Rayman et al., 1986**). The capillary blood flow in the dependent foot rises progressively with time (**Belcaro et al., 1992**) leading to an increase in the transmural pressure. In the long term this will induce a structural lesion such as thickening of capillary basement membrane. In the short term it will lead to oedema formation associated with neuropathy. Also

dysfunction has been noted in a study assessing the amplitude of flow motion (cyclical variation in blood flow owing to the rhythmical opening and closing of arterioles) which was reduced in diabetic neuropathic patients (**Benbow et al., 1995**). The sympathetic control of the microvasculature examined by spectral analysis of skin laser Doppler fluctuations has shown a loss of rhythmicity of the low-frequency oscillations, mostly under sympathetic control, which might be associated to autonomic defects introduced by neuropathy (**Rossi et al., 1990**).

Diabetic neuropathy has also been associated with paradoxical reductions in blood flow, namely failure of vasodilatation of the skin of the foot in response to body warming (**Martin, 1953**) or paradoxical blood flow responses to local heating (**Stevens et al., 1992**) The mechanisms of these findings are not known. A hypothesis might link increased sympathetic activity in the early stages of neuropathy manifested for example, in increased sudomotor function (gustatory sweating), or to hypersensitivity of peripheral vessels to local cold or circulating cathecolamines (**Flynn and Tooke, 1995**). However it is known that denervated peripheral vessels still show an autonomous tone suggestive of one or more intrinsic vascular factors which might be implicated in maintaining the vascular tone at the smooth muscle level as it has been proven for NO (**Vallance and Moncada, 1994**). In diabetes, when the Lewis' triple response to noxious stimuli was assessed, it was found that the neurogenic flare response was diminished in diabetic neuropathy (**Parkhouse and LeQuesne, 1988**). This might reflect a decreased vascular reactivity to the local release of neuropeptides from the peripheral nerve fibres (**Boolell and Tooke, 1990**).

In conclusion, the known effects of neuropathy on peripheral microvasculature can be summarised as in

Table 7.3.1 Effect of neuropathy on foot microcirculation

Increased	**Decreased**
arterio-venous shunt flow	amplitude of flow motion
basal capillary blood flow (although not known whether appropriately raised for higher skin temperature) leading in:	postural vasoconstriction pressure regulation on dependency
short term to neuropathic oedema	axon flare response
long term to thickening of capillary basement membrane	vasodilatatory responses to heating and body warming

The neurovascular responses have been studied as above, but the function of the other two components involved in neurally-stimulated vasodilatation: the endothelium and the smooth muscle, are not fully understood in diabetic neuropathy. Further studies to assess the interactions between microvascular and nervous system at endothelium and smooth muscle level are required in the understanding of the pathogenesis of the diabetic foot.

7.4. Neurovascular responses. Endothelium-dependent and endothelium-independent vasodilatation

The hyperaemic response is part of Lewis' inflammatory response to tissue injury, hence its importance in foot ulcer formation which often involves an initial injury. When a noxious stimulus is applied to the skin, the nociceptive receptors are stimulated and they send pro-dromically the nervous impulse through the C-nociceptor primary afferent fibres, responsible for transmitting the pain sensation, to the pre-ganglionic neuron and onwards to the central nervous system.

There is also an antidromic transmission through the small fibres of nerva vasorum, which will release vasoactive neuropeptides such as: substance P, CGRP along with acetylcholine, prostacyclin and bradykinin.

In endothelium-dependent vasodilatation, acetylcholine acts on the muscarinic receptors of endothelium which synthesises and releases among other vasoactive substances, an endothelium-derived relaxing factor (EDRF) = nitric oxide (NO); this then induces vascular smooth muscle dilatation.

In endothelium-independent responses, smooth muscle vasodilatation is stimulated by direct donors of NO such as sodium nitroprusside (SNP). Another source of NO which is endothelium-independent is the neurone; nitric oxide synthase (NOS) has been identified in the cytosol of peripheral as well as central neurones (**Bredt et al., 1991; Vallance and Moncada, 1994; Rand and Li, 1995**).

7.4.1 The role of nitric oxide (NO) in endothelium-dependent and endothelium-independent vasodilatatory responses

While the sympathetic nervous system serves the organism as a whole, the endothelium appears to act as a local regulator adapting blood flow to local metabolic needs. A variety of factors derived from endothelium have relaxing actions: endothelium-derived relaxing factor (EDRF) = NO, endothelium-derived hyperpolarizing factor (EDPF), prostacyclin (PGI2)) or contracting effects: prostaglandin H2 (PGH2), thromboxane A2 (TXA2), endothelin 1 (ET1) (**Rongen et al., 1994**) and they play a role in the endothelium-dependent control of the vascular tone.

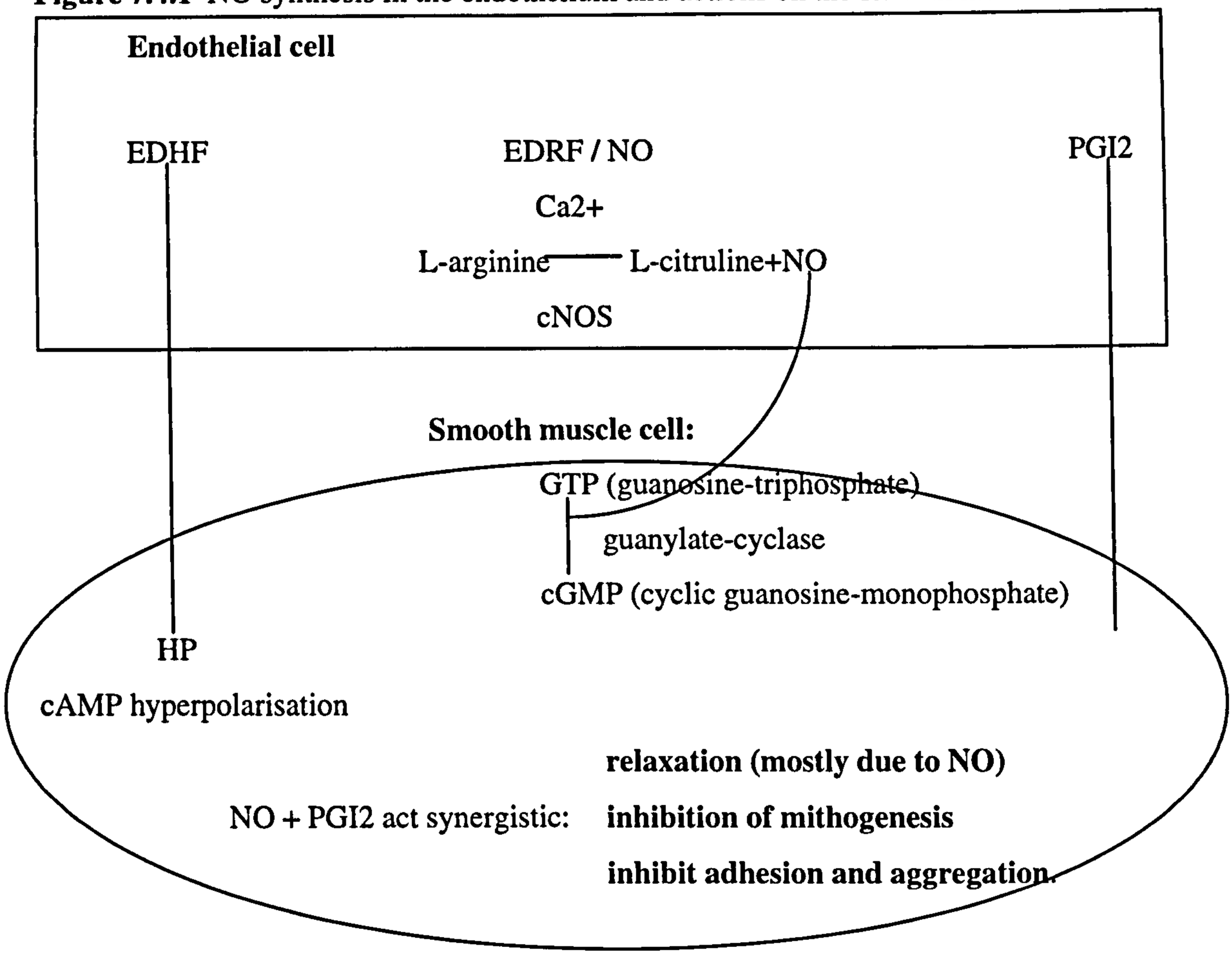
NO (*N=O) is now known to be the smallest biological product of mammalian cells. Its actions are as diverse as the tissues which produce it. NO is the product of the five-electron oxidation of one of L-arginine by the enzyme NOS. Three distinct isoforms of this enzyme with different functions representing three distinct gene products, have been isolated and purified (**Nussler et al., 1995; Martinez-Cuesta et al., 1995**). Table 7.4.1

Table 7.4.1 Human NOS isoforms: function, chromosomal and tissue localisation

Human NOS isoform	*Chromosome*	*Localisation*	*Function*
Neuronal cNOS	12	central and peripheral neurones	neurotransmitter
Endothelial cNOS	7	endothelium	EDRF
Inducible NOS	17	multiple cell types	inflammation sepsis, shock

From the endothelial cell the NO diffuses into the smooth muscle cell (which has no receptors for NO) and activates the guanylate cyclase leading to production of cyclic guanosine monophosphate, which induces vasodilatation by reducing available intracellular cytosolic calcium.

Figure 7.4.1 NO synthesis in the endothelium and actions on the smooth muscle



The basal formation of NO maintains moderate but significant vasodilatation in the systemic resistance vessels. When blood flow in conduit arteries is increased there is an augmented endothelial formation of NO, eliciting flow dependent vasodilatation (**Wennmalm, 1994**). Beside this, several vasodilators (acetylcholine, bradykinin, histamine, substance P) stimulate endothelial formation of NO.

However the NO is not the only vasodilator released from the endothelial cell to act on the smooth muscle: PgI2 acting via cAMP and EDHF inducing membrane hyperpolarisation, have synergistic effects in regards to vasodilatation and inhibition of smooth muscle proliferation which is associated with atheromatous plaque formation.

A defect at any of these steps can induce a deficit in vasorelaxation, such as the impaired endothelium-dependent relaxation to acetylcholine in diabetes, which might arise from a defect in utilisation of L-arginine by NOS for production of NO (**Pieper et**

al., 1995). However it seems that endothelium-derived hyperpolarizing factor does not contribute to the decrease in endothelium-dependent relaxation in the aorta of streptozotocin-induced diabetic rats (**Endo et al., 1995**).

In contrast, acting on the same system there are also vasoconstricting factors such as endothelin-1, thromboxan A2, prostaglandin H2, angiotensin and oxygen-derived free radicals. Likewise they are growth promoters.

Conclusion

NO is part of a complex system of relaxing and contracting factors acting on the vascular smooth muscle. However NO of endothelium-dependent or -independent origin (exogenous or neuronal) share the same common pathway to vasodilatation.

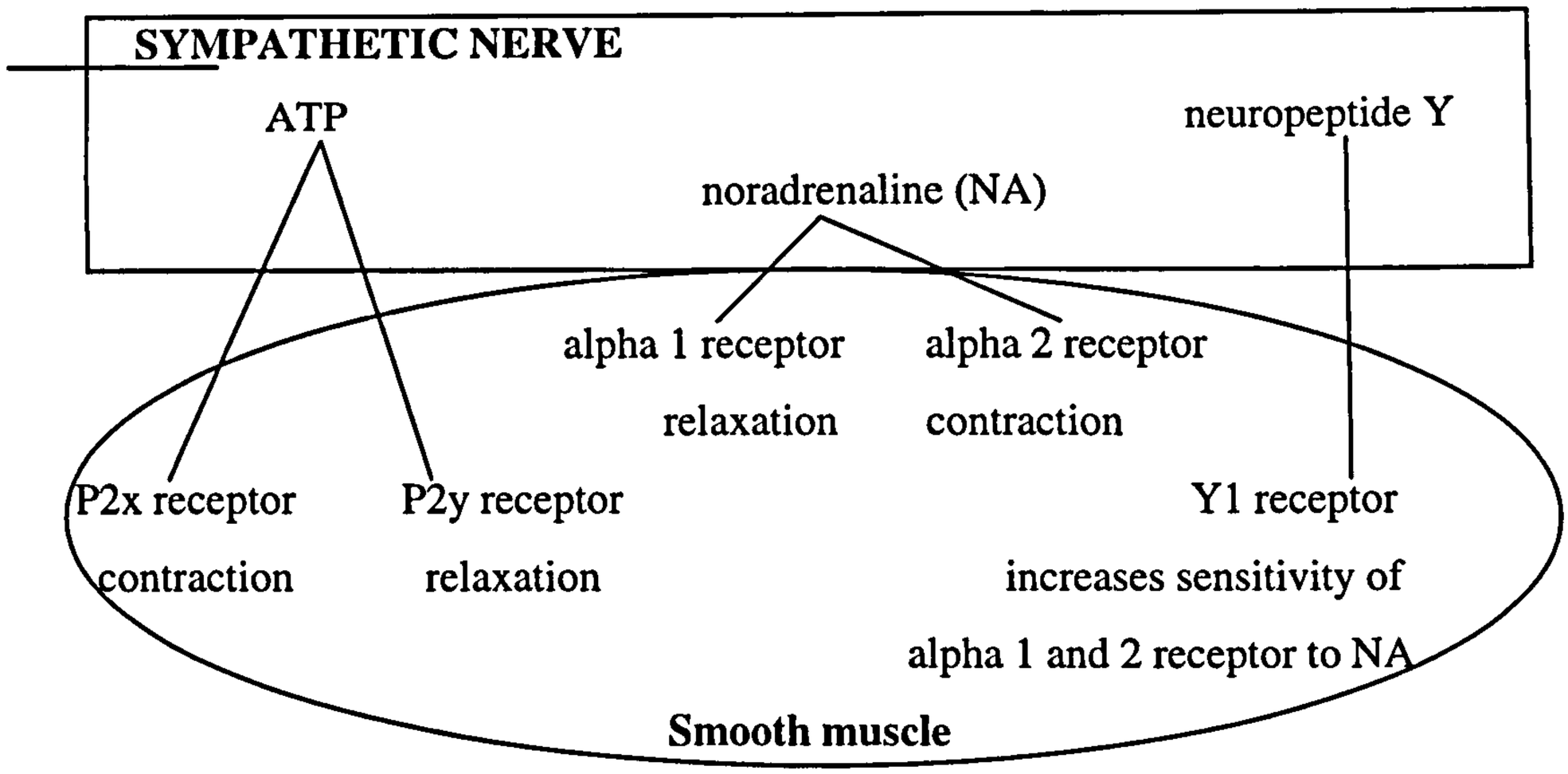
7.4.2 NO role in the interactions between the perivascular nerves and vascular wall

The perivascular nerves consist of sympathetic nerves (containing neuropeptide Y, adenosine triphosphate, noradrenaline), parasympathetic nerves (containing acetylcholine), nitrergic nerves (containing NO), sensorimotor nerves (containing vasoactive neuropeptides: substance P, CGRP=calcitonine-gene-related-peptide). These all will take part in the microvascular autoregulation controlling the release of vasorelaxing and vasoconstricting factors. If the sympathetic nerve is removed the production of endothelin-1 is increased. Therefore in a disease such as diabetic neuropathy known to affect peripheral nerve fibres, defects of neurovascular reactivity might occur.

Moreover when the levels of plasma endothelin-1 were found to be raised in diabetic rats, the endothelial-dependent relaxation was also found to be significantly attenuated (**Tada et al., 1994**).

Furthermore the same vasoactive substances released from the perivascular nerve can have a dual action, vasodilatation or vasoconstriction, according to the type of receptor to which they bind (Fig. 7.4.2).

Fig. 7.4.2 Vasoactive effects of neurotransmitters



In conclusion, in the neurovascular responses most of vasoactive compounds from the perivascular nerve act ultimately via the endothelium on the vascular smooth muscle in a very complex manner. A fine balance between vasoactive substances from the endothelium and from the perivascular nerves has to be achieved for maintaining the basal vascular tone and a normal microvascular function in healthy subjects. If any of these factors is in excess or in deficit, abnormalities of the vascular function will occur.

7.4.3 Increased oxidative stress in diabetes and its effect on NO and endothelial function

In diabetes endothelial cell impairment and increased vasoconstriction might involve a mechanism which activates the PGH2/TXA2 receptors (**Tesfamariam et al., 1995**). This impairment has been shown to be restored by blockade of PGH2/TXA2 receptor or superoxide dismutase suggesting that PGH2, TXA2 and/or superoxide anion contributes to this abnormality (**Dai et al., 1993**).

The effects of elevated glucose are exacerbated by increased aldose-reductase activity leading to depletion of NADPH and generation of reactive oxidants (**Tesfamariam, 1994**). Because NADPH is required for generation of NO from L-arginine , the depletion of NADPH may lead to reduced nitric oxide formation.

It has also been hypothesised in diabetes that oxygen-derived free radicals generated during both glucose autooxidation and formation of advanced glycosilation end products may interfere with NO action and attenuate its vasodilatatory activity. The oxidative injury may also be increased in diabetes because of weakened defence due to reduced endogenous antioxidants (vitamin E, reduced gluthathione) (**Giuliano et al., 1995**). Findings to support this hypothesis show that intracellular hydroxyl radicals mediate injury to endothelium-dependent relaxation in diabetic rat. (**Pieper et al., 1993**) and that advanced glycosylation products quench nitric oxide and mediate defective endothelium-dependent vasodilatation in experimental diabetes (**Bucala et al., 1991**).

In conclusion, in diabetes an increased oxidative stress occurs resulting in endothelial cell dysfunction. Hyperglycemia leads to NADPH depletion with a subsequent decrease in NO production. Furthermore advanced glycosylation end products quench nitric oxide inducing abnormalities of vasodilatation.

7.4.4. The effect of diabetes on endothelium-dependent and endothelium-independent responses

In diabetes cumulative effects of oxidative stress on endothelial cell together with complex interrelationship of cyclooxygenase catalysis, increased protein kinase C activity and increased flux through the polyol pathway (**Cameron et al., 1993**) would have an effect on the endothelium-dependent relaxation and/or smooth muscle contraction .

In animal studies, a selective impairment of receptor-mediated endothelium-dependent relaxation to acetylcholine has been reported in isolated resistance arteries of the streptozotocin-induced diabetic rat. These results suggest that the ability of endothelium to relax arteries via nitric oxide may involve a defect of a specific signal transduction pathway leading to reduced production of nitric oxide (**Taylor et al., 1995**) In NIDDM, in aortae from non-insulin-dependent diabetic rats impaired endothelium-dependent vasodilatatory responses resulted in increased noradrenaline-induced contractions (**Karasu et al., 1994**). Moreover in vitro studies using human arteries obtained from patients undergoing coronary artery by-pass surgery showed that whereas endothelium-independent responses to SNP were not influenced by NIDDM, this produced a deficit in the vasorelaxant activity of endothelium (**Karasu et al., 1995**).

However in patients with NIDDM but also with some diabetic complications, impaired endothelium-dependent and independent vasodilatation was reported (**McVeigh et al., 1992;Morris et al., 1995**).When the vascular reactivity was compared in a IDDM versus a NIDDM rat model, a depression of endothelium-dependent responses was found in both of them, the IDDM model had also increased beta-adrenergic reactivity, whereas the NIDDM model had increase responses to serotonine (**Feletou et al., 1994**).

In IDDM, in vitro studies using isolated resistance vessels from patients with insulin-dependent diabetes mellitus found also an impaired contraction and endothelium-dependent relaxation suggestive of a defect in the endothelial cell acetylcholine receptor excitation-coupling (**McNally et al., 1994**). In IDDM patients conflicting reports were published showing: impaired (**Johnstone et al., 1993**) or preserved (**Smits et al., 1993**) endothelium-dependent vasodilatation in uncomplicated patients with insulin-dependent diabetes mellitus. Others have shown an inhibition of nitric oxide synthesis with blunted vasoconstriction only in forearm vasculature of complicated insulin-dependent diabetic patients: with microalbuminuria (**Elliott et al., 1993**).

In complicated diabetic patients, such as diabetic men with impotence a significantly reduced response to endothelium-dependent vasodilators was reported in isolated cavernosal smooth muscle, but not to endothelium-independent vasodilators suggesting that the endothelial dysfunction seems to play an important role in diabetogenic impotence (**Kim et al., 1995**).

Conclusion

Most of these studies showed abnormal endothelial function with preserved smooth muscle function in diabetes. There are only a very few studies reporting endothelial dysfunction and also an alteration in the responsiveness of smooth muscle in mongrel dogs with long-duration diabetes and probably complications such as neuropathy (**Sarioglu et al., 1993**) and in patients with hereditary sensory radicular neuropathy in the areas of defective neurogenic inflammation (**Westerman et al., 1992**).

From recent research it has become apparent (**Harrison et al., 1995**) that abnormal endothelium-dependent vasodilatation leading to altered regulation of the vasomotion precedes atherosclerosis in large vessels; whereas in microcirculation, in which atherosclerosis does not develop, it is related with the development of other

microangiopathic complications in diabetes. Therefore, taking into account the close inter-relation between the perivascular nerves and the endothelial and smooth muscle function, the necessity raises for further studies to be undertaken in order to assess the endothelium-dependent vasodilatation (as a test of endothelial function) and endothelium-independent vasodilatation (as a test of smooth muscle function) in the presence of diabetic neuropathy. This evaluation of two major risk factors for the diabetic foot, such as neuropathy and microangiopathy, should bring further understanding in the foot ulceration pathogenesis.

7.5 Neurovascular responses assessment by a non-invasive method: iontophoresis

As outlined in the preceding section, the mechanism responsible for neurovascular responses in the skin, as by example in nocifensor responses, involves the three elements:

1) polymodal nociceptors, primary afferent fibres and NANC (non-adrenergic-non-cholinergic) nerves.

2) microvascular endothelium

3) microvascular smooth muscle.

Testing the neurovascular function therefore ought to assess:

1) the nerve function using standard tests of nerve fibre: vibration perception threshold, thermal perception threshold etc. or noxious transcutaneous electrical stimulation (TENS) evoking the axon reflex dilatation of skin microcirculation which examines indiscriminately the three components of the nocifensor response.

2) the endothelium function using methods of endothelium-dependent vasodilatation, such as acetylcholine (ACh) iontophoresis.

3) the smooth muscle function using methods of endothelium-independent vasodilatation to direct donors of NO, such as iontophoresed sodium nitroprusside (SNP) (**Furchgott, 1984**).

Iontophoresis for delivery of vasoactive substances plus laser Doppler flowmetry for subsequent vasoreactivity measurements form together a battery of tests recommended for the non-invasive assessment of neurovascular responses. Basic principles will be discussed together with a summary of recent observations using these techniques to investigate the skin microvasculature.

7.5.1 Iontophoresis principle and limitations

Iontophoresis (or ion transfer) is a non-invasive technique of drug delivery which allows the local transfer of charged substances (ions) across the skin using a small electric current.

It is preferred in studies assessing the vasodilatatory responses of the skin superficial microcirculation because no demonstrable spread takes place in subcutaneous or deeper structures except in special circumstances such as ischaemia or when very strong currents are used, which also would be likely to induce an axon reflex **(Harris, 1978)**.

Having the advantage of a non-invasive and uniform method which is free of unwanted side-effects and minimises trauma or risk of infection, iontophoresis is an important alternative to needle. Furthermore when testing solely the endothelium-dependent and smooth muscle vasodilatation is even important to avoid triggering an axon reflex which will involve also the neurogenic flare.

This is the reason why iontophoresis of small currents (<=100 microAmpers) is preferred to intradermal injection which is an invasive technique inducing a skin injury and delivering the active substance at variable depths in or under the skin.

The iontophoresis term comes from the Greek derivative and indicates the transfer of ions into the body, in our case into the skin. In studies using potentiometry and X-Ray fluorescence it has been shown that iontophoresis does not result in superficial migration of the applied ions on the skin from one pole to another but leads to penetration into the skin **(Puttemans et al., 1982)**.

The substances used for vasodilatation are in a stable form; in order to became active ions they need to be dissolved in a vehicle, usually in distilled, deionised water which does not conduct electric current in its pure state **(Westerman et al., 1988)**. However recently a vasodilatatory effect has been reported to be introduced by the vehicle alone: more for SNP (which used water as a vehicle) than for ACh (which used mannitol as a vehicle) **(Morris et al., 1995)** underlying the importance of choosing an

appropriately inert vehicle for iontophoretic studies of neurovascular function or deducting the vehicle response from the total vasodilatation. Electric potential by itself does not change the skin permeability (**Schaefer et al., 1982**).

When salts, acids or bases are dissolved in water, the resulting aqueous solution becomes a conducting liquid called electrolyte containing positive and negative-charged ions of the initial substance. The direct current passes through the electrolytic solution by migration of ions: the positive ions travel towards the negative pole (anode) and the negative ones towards the positive pole (cathode).

The polarity of the active electrode is determined by the ion to be introduced into the skin: e.g. for acetylcholine chloride, anodal currents are used to transfer the cathion (Ach+) or for sodium nitroprusside cathodal currents are used to deliver the anion nitroprusside (NP-). The substances are usually placed under a chamber fixed at the surface of the skin with double-adhesive tape, which is connected to an iontophoresis device. This is a constant current generator, for which the chamber represents the active electrode.

The range of response to iontophoresis does not depend on the concentration of the electrolyte solution but on the total charge applied accordingly to Faraday's law (the amount of substance deposited at each electrode is proportional with the amount of electricity passing through the system).

Therefore, the iontophoresis is a local and non-invasive method for drug delivery. It consists in the transfer of active substances ions into the body proportional with the total charge of electric current applied.

<u>Sources of variation and dose-response curves</u>

Due to the complexity of factors involved during the process of iontophoresis through living tissues theoretical predictions based on Faraday's law are virtually impossible (**Tyle, 1986**).

Experimental variables include:

- pH: changes in pH of the fluid at the driving electrodes produced only minor changes on the uptake of the ions by the tissue.
- ionic strength might influence the uptake although there are not many reports to support this supposition.

- size and charge of the electrodes: greater amount of drug is introduced by bigger electrodes.
- type of electrode: those which have a good adherence to the skin surface would increase the uptake.
- duration and intensity of current: varying one or another can help maintain/ change the amount of ions introduced by iontophoresis.
- resistance of the skin can vary widely at different sites of the body; using the same testing site will reduce variability although individual variations might occur.
- season: in summer responses tend to be smaller probably due to increased thickness of the epiderm.

Individual variables:

- sex: female subjects have larger responses probably due to differences in epidermal thickness and structure.
- regional variations: gradient of response in upper and lower limbs.

Thus in clinical studies of neurovascular function in diabetic patients Westerman et al., **(1988)** have determined dose-response curves to increasing intensity of iontophoretic stimulus by varying the intensity of current or the duration of iontophoresis application but they maintained the other variables constant:

$q = I \times t$

where q= charge given in millicoulombs (mC)

I= current intensity given in miliAmpers (mA)

t= time given in seconds

In a study assessing the endothelial function (by iontophoresis of acetylcholine) and the smooth muscle function (by iontophoresis of sodium nitroprusside) in the forearm of NIDDM patients cumulative dose-responses were used (**Westerman et al., 1988**). Repeated stimuli of equal intensity and duration plus a last one of double intensity and same duration were applied. The vasodilatatory response for acetylcholine reached the plateau quicker than for sodium nitroprusside whose response was slower, but more persistent (**Morris et al., 1995**). However one has to be careful in using excessive current intensity (> 1 mA) because this can directly injury the skin when applied for a longer period of time or induce an axon reflex even when short duration stimuli are applied (**Magerl et al., 1990**). Similar studies have been done in diabetic animals and humans for the development of a battery of neurovascular tests **(Westerman et al., 1987; 1988)**

7.5.2 Recent studies of iontophoresis use in the study of skin responses

Interest and research in this technique has increased because of therapeutic uses in different areas of medicine e.g. in cystic fibrosis, in dermatology for the diagnosis and treatment of various skin disorders (**Sloan et al., 1986**); being extensively used in the assessment of inflammatory, sudomotor and vasomotor cutaneous responses.

Cutaneous inflammatory responses

Histamine iontophoresis has been demonstrated to be a reliable model for the study of inflammatory skin responses (**Magerl, 1990**).

Noradrenaline iontophoresis used in a study which has shown that noradrenaline and sympathetic stimulation increase nociceptor discharge in inflamed skin suggesting that sympathetic neural activity might increase pain associated with skin damage in healthy subjects (**Drummond, 1995**).

Cutaneous sudomotor responses

Also iontophoresis has been used widely for tests of sudomotor function such as the classical pilocarpine iontophoresis test used in the diagnosis of cystic fibrosis.

In diabetes, muscarinic receptors situated on the sweat glands were directly stimulated by iontophoresis of acetylcholine and then their response was compared to the axon reflex-mediated sudomotor responses via nicotinic receptors. Overrepresentation of large sweat droplets was found in patients with mild diabetic neuropathy, while patients with severe neuropathy had a markedly reduced density and small size droplets (**Kihara et al., 1993**).

Also the failure of sudomotor axon reflex preceded the defect in direct response suggesting that abnormality of sympathetic nerve component occurs early in diabetic neuropathy. Likewise in another study of basal and stimulated sweating by acetylcholine iontophoresis, in diabetes showed that both low- and high- amplitude responses are seen in diabetic neuropaths, the latter being suggestive of denervation hypersensitivity (**Levy et al., 1991**).

A reduction in the sudomotor response to acetylcholine iontophoresis has been found only in late stage neuropathy, whereas the neurogenic response to histamine iontophoresis seems to be decreased in all stages of neuropathy suggesting that is more sensitive in detecting impairment of unmyelinated fibres affected early in the course of neuropathy (**Lang et al., 1995**).

Cutaneous vasomotor responses

Physiological studies showing the role of baroreflex control on the cutaneous active vasodilator system in humans (**Kellogg et al., 1990**) used the iontophoresis of bretyllium, which is a selective blocker of noradrenergic vasoconstrictor nerves in the skin (**Kellogg et al., 1991**). Furthermore fundamental research on adrenoceptors, which have demonstrated that postjunctional alpha-adrenoceptors in human finger skin vessels are of both alpha-1 and alpa-2 subtypes (**Linblad et al., 1986**) and that vasoconstriction on local cooling in human finger skin is mainly mediated by alpha-2 adrenoceptors (**Ekenvall et al., 1988**), used a iontophoresis of a variety of adrenoceptor agonists: (phenilephrine or B-Ht 933: alpa-2 agonist) and alpha-1 (doxazosine) and alpa-2 (rauwolscine) antagonists .

Conclusion. Limitations and advantages of iontophoresis

The iontophoresis process consists in passing polar drugs across the skin using small, direct currents (**Trubach et al., 1972**). The exact concentration and distribution of active ion is not known precisely since a determined charge (product of current and time) has to transport the ions through the skin, which has variable mechanical and electrical properties (**Edelberg, 1970**). However if standard stimuli are used in standard conditions the effect of this sources of variation can be minimised. Thus iontophoresis has been extensively used in the assessment of inflammatory, sudomotor and vasomotor cutaneous responses. Specifically in studies of skin vascular reactivity, dynamic changes in blood flow following iontophoresis of vasoactive substances, should be determined ideally using a non-invasive method of blood flow measurements, such as laser Doppler flowmetry (LDF).

7.6 Laser Doppler flowmetry: a non-invasive method of dynamic blood flow measurements in neurovascular responses

Most of the techniques for blood flow measurement have the disadvantage of being invasive. In contrast Laser Doppler flowmetry (LDF) is a non-invasive test of skin blood flow. Furthermore LDF has a special characteristic: is sensitive to dynamic changes in the blood flow, therefore being of potential use in studies of vascular reactivity.

The low power laser used by the LDF generates a non-noxious beam of infrared light transmitted through an optical fibre to illuminate a small area on the skin. The red blood cells moving inside the microvessels of the illuminated skin scatter the photons generated by the laser and they will undergo a frequency shift according to the Doppler principle. The resulting light is collected and transmitted to a photodetector. The photodetector signal is amplified and processed by an analogue processor then the signal is sampled and further processed by the digital processor which will perform the interface and display functions providing a reading proportional to the local blood flow.

The resulting measurement is expressed in arbitrary units of blood flux, more correctly as blood cell flux - which can be argued that is a more realistic measurement since the flow of red blood cells delivers the oxygen to the tissue and not the simple plasma (fluid) flow. (**Almond, 1994**). The measurement is continuous and has spatial and temporal resolution so dynamics associated with local skin blood flow regulation can be followed concomitantly on the screen. These perfusion data are automatically stored by the computer and could be printed out. Recently it has also become possible to separately quantitate the two components of blood flow: red blood cell concentration and red blood cell speed and to use new Laser Doppler techniques such as dual channel systems (**Obeid et al., 1966**) or laser Doppler imagers (**Wardell et al., 1991**) allowing a better understanding of blood flow changes and the complexities of the microcirculation.

7.6.1 Standardisation of LDF instruments

LDF by using Doppler shifts in the range of helium-neon laser light wavelength 632.8nM or infrared 760-800nM would be sensitive to all microscopic movements. Those devices with two optic fibres for pick up of the reflected signal and differential

recording have been more sensitive and less prone to movement artefacts (**Nilsson et al., 1987, Johansson et al., 1987**). Filtering and improvements in fibre optic cables have further reduced this problem (**Kilpatrick et al., 1988; Salerud et al., 1987**).

Comparison of LDF with accepted and accurate methods of blood flow measurements showed good correlations with microsphere flowmetry (**Kiel et al., 1985; Kvietys et al., 1985**), 133 Xenon clearance (**Stern et al., 1977**) and electromagnetic flowmetry (**Shepherd et al., 1982; 1983**). When LDF was compared to optical plethysmography and heat thermal clearance the results suggested that the different methods measured blood flow at different depths in the skin vascular beds (**Saumet et al., 1986**).

One of the main problems with calibration of LDF is the lack of suitable standard against which it may be compared because all the methods used for comparison have their own variability. The moderate correlation found with these other methods of blood flow is not surprising as the measurements are done in different ways and sometimes in different vascular beds.

7.6.2 Limitations of the LDF method

Different techniques of blood flow measurement have various degrees of variability and a reproducible standard of blood flow would be required when comparisons among them and LDF are made. Unfortunately this standard has not been yet established; therefore the necessity of variability tests in each study using LDF.

The skin microcirculation has large periodic oscillations (**Seifert et al., 1988**) due to cyclical opening and closing of the arterioles related to the sympathetic tone, inducing oscillations in tissue perfusion within tissue regions of the order of 1mm3 (which is the usual sample size for LDF). The oscillations are thought to be caused by vasodynamic activity in the precapillary vascular bed of the skin (**Fagrell, 1985**). Also the microcirculatory architecture of the skin is not homogenous with possible effect on LDF variability.

When measuring red cell flux, the measurements ought to be averaged over long periods of time or from independent sites assessed simultaneously **(Borgos, 1994)**. It is recommended to estimate where possible the relative changes in blood flow in response to a provocation and not rely entirely on the absolute measurements of basal blood flow.

Factors which can influence the LDF reproducibility are:

a) **Individual variables of the subjects:**

- sex and age
- time of testing (sympathetic tone is changing during the day)
- anxiety (vasoconstrictor tone)
- current medication and/or ingestion of vasoactive substances: tea, coffee etc.
- basal blood flow
- site to site variability.

b) **Biological variables:**

1) *skin and adjacent tissues variables*:

- skin thickness, pigmentation, presence of hair and freckles.
- skin and ambient temperature
- sweat pore distribution and density
- volume of tissue in which the microcirculation is assessed because of uncertainty about the depth of laser penetration.

2) *microvascular variables*:

- capillary density
- capillary flow distinguished from arterio-venous flow
- microvascular bed distribution and density
- permeability differences
- presence of non-cellular elements such as lipids droplets in the vessels assessed
- haematological features such as the haematocrit which might affect the LDF measurements in the absence of flow.

c) Technical variables:

1) Equipment:

- variable sensitivity to any microscopic movements.
- variable voltage output for standard calibration signal
- laser gain settings, time constant, filters
- laser probe at variable distance from the skin
- analogue chart recorder settings
- response increase (% rise in laser Doppler flux) depends on the basal blood flow level which can be influenced by biological variables.

2) Operator error: - different operators performing and/or analysing the recordings.

In clinical use LDF reproducibility can be improved by a careful choice of protocol in order to minimise the effect of some of these variables. Matching patients and healthy subjects taken into the study for age, sex and when possible for lipids and haematological profile helps in reducing the variability. Also testing all the subjects at the same time of day in a temperature controlled and quiet room and asking them to abstain from previous ingestion of vasoactive substances or medication would contribute to a decrease in the coefficient of variation.

The effect of variable skin thickness can be reduced by choosing the same testing area which will be free of hair, freckles, pigmentation in all the subjects of study. This achieves some control on the density of sweat glands but also on the density of capillaries versus the density of arterio-venous shunts which are known to be more frequent in some areas (e.g. the pulp of the toes) plus will provide an assessment of the same vascular bed in all subject.

As regards the technical variables, using only one type of laser Doppler flowmeter with a single wavelength would allow a quasi-constant depth of penetration and therefore a comparable volume of tissue and its microcirculation will be assessed; as well as maintaining constant equipment characteristics and a comparable sensitivity to all microscopic movements. If only one operator is involved with the study, the variability can be reduced furthermore.

As the response increase depends on the basal blood flow and measurements of absolute levels of basal blood flow might be variable, ratioing the peak blood flow to basal blood flow might be recommended. It has been shown that this ratio remains constant, despite basal blood flow variations (**Gardner-Medwin and MacDonald et al., 1995**). Furthermore the ratio of peak to basal blood flow would also be independent of other variables such as differing skin temperatures which could also affect basal blood flow.

Conclusion

The most potent use of LDF lies in its sensitivity to quantify relative changes in blood flow in response to vascular stimulation. The variability of LDF measurements is still a question which requires careful methodological standardisation, in order to minimise the effects of technical, individual and biological variables. In such studies the final response measured by LDF is microvascular vasodilatation or constriction probably involving only epidermal microvessels, particularly precapillary arterioles or postcapillary venules (**Westerman et al., 1988**). Therefore LDF should be particularly advantageous in assessing neurovascular reactivity (responsiveness and sensitivity) of the cutaneous microcirculation.

7.6.3 Recent studies of LDF use in testing neurovascular reactivity in diabetes

Reactive hyperaemia

In diabetes, numerous studies have employed LDF for assessing reactive skin hyperaemia in response to a standard ischaemic stimulus and have demonstrated the value of LDF in quantitating dynamic vasodilator responses when trying to measure subtle functional disturbances of microcirculation resulting from chronic peripheral arterial disease (**Walberg et al., 1990**).

In diabetic versus non-diabetic patients with peripheral vascular disease the ratio between capillary blood cell velocity measured by videophotometric capillaroscopy and LD flux (representing distribution of flow between nutritional and non-nutritional blood compartments) was found to be reduced suggesting increased risk of foot ulceration (**Jorneskog et al., 1995**).

These studies also demonstrate the reasoning for LDF most efficient use: to measure changes without attempting to extrapolate absolute flow data. Post-ischaemic hyperaemia tests in diabetic patients reveal cutaneous microcirculatory changes which are associated with the presence of diabetic microangiopathic complications such as retinopathy (**Tur et al., 1991**).

However in long-duration IDDM the peak flow (which is a predominant smooth muscle response) occurring post- ischaemia was impaired, but this impairment was not associated with the presence of microangiopathy or with recent blood glucose control suggesting a specific defect introduced by IDDM per se (**Walmsley et al., 1990**).

Moreover when diabetic neuropathy is present a shortened time to half peak flow, representing a speedy vasodilatation, reflected a reduction in the viscoelasticity of the arterial wall. Furthermore when the veno-arteriolar (VAR) response to standing was measured by LDF, an impairment of VAR was found in diabetic patients with neuropathy suggesting that the postural control of blood flow in the skin of the foot is decreased (**Belcaro et al., 1991**).

<u>Reactive vasoconstriction</u>

Studies of reactive vasoconstriction to different stimuli such as inspiratory gasp, ice-water immersion, spring-loaded pin-prick or postural change, which depends on an intact peripheral nervous system were also selectively using LDF. Inspiratory gasp vasoconstrictive responses as assessed by LDF were considered to be sensitive techniques for evaluating sympathetic efferent function (**Valley et al., 1993**) and could be used as tests for peripheral sympathetic neuropathy identification (**Wilson et al., 1992**). In diabetic neuropathic patients a lack of vasomotor activity was found to

correlate with increased blood viscosity but not with the increased aggregation index **(Zioupos et al., 1993)**.

Furthermore impaired posturally induced vasoconstriction was found even in postpubertal diabetic children most of them being free of complications **(Shore et al., 1994)**. Indeed the vasoconstrictor responses to inspiratory gasp and arm cold challenge ,assessed by LDF, were proven to decline with age even in non-diabetic controls suggesting once more the hypothesis that diabetes and moreover diabetic neuropathy, act as an accelerated ageing process **(Khan et al., 1992)**

Maximum hyperaemic response to heating

Detection of microvascular impairment by using laser Doppler flowmetry in type 1 diabetes, before complications became apparent, was demonstrated in a study measuring the hyperaemic response to local heating (44°C) **(Wilson et al., 1992)**. Also it has been shown that an impaired maximum hyperaemic response to heating occurs even in prepubertal diabetic children in the absence of clinically detectable microangiopathy **(Shore et al., 1991)**.

Autonomic dysfunction as investigated by LDF measurements in response to hyperthermal stimulus has been shown to occur early in the course of NIDDM **(Koltringer et al., 1992)**. Diabetic neuropathy was shown in another LDF study to introduce a paradoxical decrease to local heating to 44 C in arteriovenous flow **(Stevens et al., 1991)**.

Neurogenic responses

Neurogenic inflammation, mediated by nociceptor C fibres, is part of the acute neurovascular response to injury producing the axon reflex flare. In a study by Walmsley and Wiles **(Walmsley et al., 1991)** Laser Doppler flowmetry was used to measure the flare response induced by the electrophoresis of a ring of acetylcholine solution into dorsal foot skin and found it greatly reduced especially in patients with a

history of foot ulceration. Furthermore impairment of this nociceptor C fibre response can develop before clinical large-fibre neuropathy and could itself predispose to foot complications.

In another study of LDF in the foot, acetylcholine mediated endothelial response to noxious stimuli (induced by mechanical stroking of the skin) was decreased, but smooth muscle reactivity was not tested (**Parkhouse and LeQuesne, 1988**).

Another interesting study (**Lang et al., 1995**) compared the sensitivity of histamine induced neurogenic vasodilatation (measured by LDF) to acetylcholine induced sudomotor axon reflex (measured by hygrometry) in diabetic neuropathic patients. The histamine induced vasodilatation was significantly impaired in early stages of neuropathy. This can be used as an acceptable test of small nerve fibre impairment, which occurs early in progression of neuropathy (**Said et al., 1983**)

Furthermore in order to gain insight into the mechanisms of reduced skin hyperaemia to local injury, another group has injected intradermally capsaicin and substance P, known as a potent vasodilator involved in the axon reflex flare response, and evaluated the response by LDF. In diabetes impaired hyperaemia to substance P but not to exogenous capsaicin, was demonstrated. This might reflect a decreased vascular reactivity to the local release of neuropeptides from the peripheral nerve fibres (**Boolell and Tooke, 1990**).

Conclusion

Laser Doppler flowmetry (LDF) has proved to be a useful non-invasive test of blood flow in skin microvessels, allowing a constant monitoring of the blood flow. Moreover LDF is able to assess relative changes in the blood flow under dynamic circumstances, therefore being particularly beneficial in studies of neurovascular reactivity such as: reactive hyperaemia and vasoconstriction, maximum hyperaemic response to heating and neurogenic vasodilatation, all of which were extensively investigated in diabetes.

7.7 Rationale for studying neurovascular reactivity in diabetes

Therefore the combination of drug iontophoresis with LDF utilises their strongest features namely that iontophoresis is not invasive and is confined to the epidermis, and LDF is also non-invasive and is very sensitive in detecting dynamic changes in the blood flow (**Westerman et al., 1988; Lindblad et al., 1986**).

These tests together are recommended for the assessment of vascular reactivity in the skin providing a convenient way to evaluate the effects of transdermally applied vasoactive substances without risking the central effects of the substance to influence the registered blood flow.

The neurogenic component of the neurovascular response has been thoroughly researched and indicates that diabetic neuropathy plays an important role in reducing the ability of foot to defend itself against noxious stimuli because of a reduced axon reflex.

Further studies to examine the effects of neuropathy on the vascular: endothelium-dependent and endothelium-independent components of the neurovascular response are needed and this chapter will describe two studies of neurovascular responses in patients with neuropathy, with or without diabetes.

The role of microcirculation vascular reactivity as a factor involved in the mechanism of foot ulceration, needs to be evaluated in an attempt to go a step further in the understanding of foot ulceration aetiology.

7.8 Endothelium-dependent and endothelium-independent responses in diabetic patients with peripheral neuropathy

7.8.1 Introduction

Neuropathy leads to considerable pathology in the diabetic foot, in which the blood flow and neurovascular responses are abnormal. Abnormalities introduced by neuropathy in the diabetic foot can lead ultimately to foot ulcer formation and furthermore can have a negative impact on the tissue repair and wound healing potential.

The neural component of the neuro-vascular responses has been studied in neuropathy, but their vascular component: the endothelial and smooth muscle, function in neuropathy is less well known. Although endothelium-dependent and endothelium-independent vascular responses have been extensively studied in diabetes, they have been not fully investigated in diabetic patients with neuropathy.

Recently there has been increasing interest in the regulation of the vascular tone by perivascular nerves and endothelial cells (**Burnstock and Ralevic, 1994**). In endothelium-dependent vasodilatation, acetylcholine acts on the muscarinic receptors of endothelium which releases nitric oxide (NO); this then induces vascular smooth muscle dilatation. In endothelium-independent responses, smooth muscle vasodilatation is stimulated by direct donors of NO such as sodium nitroprusside (SNP). Another source of NO which is endothelium-independent, is the neurone (**Bredt et al., 1991; Vallance and Moncada, 1994; Rand and Li, 1995**). In patients with diabetic neuropathy and possibly with subsequent neural depletion of NO, abnormal responses might occur.

<u>Aim of the study</u>

The aim of this study was to investigate vascular responses to acetylcholine and sodium nitroprusside by iontophoresis in patients with diabetes mellitus and with severe neuropathy.

7.8.2 Patients

Three groups of subjects were studied: 10 patients with diabetic neuropathy, 10 diabetic patients without neuropathy and 10 non-diabetic control subjects.

They were matched for age, sex and type of diabetes. The HbA1c was similar in the three groups of diabetic patients. Foot pulses were present in all subjects.

Neuropathy was defined by the absence of ankle reflexes accompanied by abnormal vibration perception threshold (VPT> 25 Volts) measured with a Biothesiometer (Vickers, Ohio, USA).

Six out of ten patients with neuropathy had a history of foot ulceration although none of the neuropathic patients had active ulcers at the time of the study. None of the subjects had peripheral oedema.

Seven patients with neuropathy had also diabetic retinopathy and five neuropathic patients had proteinuria. In the diabetic control group a similar number of patients with retinopathy and proteinuria was selected.

As there may be important differences in the microvascular responses between IDDM and NIDDM patients, it was decided, for analysis purposes, to assess the trends present in the NIDDM patients, as a separate group.

Eight NIDDM patients with peripheral neuropathy and 7 NIDDM patients without neuropathy were studied versus 10 non-diabetic control subjects. Six out of eight patients with neuropathy had a history of foot ulceration although none of the neuropathic patients had active ulcers at the time of the study.
None of the subjects had peripheral oedema.

Table 7.8.1 Clinical details of all subjects

	Controls (C)	Diabetic Controls (DbC)	Neuropathic patients (Np)
Number	10	10	10
Sex (F/M)	4F / 6M	5F / 5M	4F / 6M
Age (years)	48.2±11.5	56.8±14.7	51.7±15.2
IDDM / NIDDM	-	3 / 7	2 / 8
Diabetes duration (years)	-	9.1±7.7	12.5±6.5
Plasma glucose (mmol/l)	-	9.6±4.5	10.2±5.1
HbA1c (%)	4.4±0.8	8.9±2.6	9.6±1.4
VPT (volts)	6.4±1.3	9.2±3.7	41.9±9.6
Diabetic retinopathy	-	6	7
Proteinuria	-	4	5
History of foot ulceration	-	-	6

Mean ± SD VPT = vibration perception threshold

Six patients with neuropathy had also diabetic retinopathy and five neuropathic patients had proteinuria.

In the diabetic control group a similar proportion of patients with retinopathy and proteinuria was selected.

Table 7.8.2 Clinical details of the NIDDM patients in which neuro-vascular responses were measured

	Controls (C)	**Diabetic Controls (DbC) with NIDDM**	**Neuropaths (Np) with NIDDM**
Number	10	7	8
Sex (F/M)	4F / 6M	3F / 4M	3F / 5M
Age (years)	48.2±11.5	58.1±13.1	52.3±13.7
Diabetes duration (years)	-	8.9±1.2	13.7±5.0
Plasma glucose (mmol/l)	-	10.1±2.9	10.8±4.3
HbA1c (%)	4.4±0.8	9.1±1.9	9.9±1.0
VPT (volts)	6.4±1.3	9.7±2.5	43.1±8.4
Proteinuria	-	4	5
History of foot ulceration	-	-	6

Mean ± SD VPT = vibration perception threshold

There were no statistically significant differences between the NIDDM subgroups and the all diabetic groups.

All patients had their usual dose of insulin or tablets in the morning of the experiment and they abstained from caffeine, alcohol and tobacco overnight.

Informed consent was obtained from all the subjects and the project had been approved by the King's Healthcare Ethical Committee.

7.8.3 Methods

The changes in skin blood flow were assessed with a Moor Laser Doppler (Moor Instruments Ltd., Axminster, UK). The probe of the Laser Doppler was attached to a plastic chamber placed on the dorsum of the foot. The patients were lying down on a couch at 1m above the ground, in a room with an ambient temperature of 22-23°C. The left foot was tested in all patients in order to standardise the method for statistical reasons and knowing that all the neuropathic patients had symmetrical peripheral neuropathy.

The iontophoresis technique was used in this study because this is the only technique which allows the drug application solely to the superficial vessels of the skin. Intradermal injection techniques deliver drugs at unknown depths and being invasive themselves induce a flare response.

The dorsum of the foot was chosen as the testing site because diabetic neuropathy affects first the longest nerve fibres which innervate the feet and also because it has been shown that the skin thickness on the dorsum of the foot in neuropathic patients is not increased (**Forst et al., 1994**). None of the subjects had peripheral oedema. The skin of the dorsum of the foot was prepared for iontophoresis and cleaned with an alcohol swab (**Morris et al., 1995**).

The round iontophoresis chamber was then fixed to the skin by a double-sided adhesive disc. The chamber was designed with a space in the middle to accommodate the Laser Doppler probe and with a ring-channel situated at 5 mm from the margin of the chamber. The substances to be iontophoresed were placed with a fine pipette under the probe on the surface of the skin.

The chamber was considered to be the active electrode and was connected with a battery-operated iontophoresis device. The indifferent electrode was a wet band applied to the ankle. A small constant current (100μA) transported the ions of substance from the active electrode to the indifferent electrode through the superficial layers of the skin. The iontophoresis device would deliver a constant intensity of electric current adjusting for each individual skin resistance.

To transfer the drugs into the skin the polarity of the active electrode had to be the same charge as the drug. Therefore, for acetylcholine chloride (Iolab, a Johnson & Johnson Co., Bracknell, Berkshire, UK) anodal currents were used to transport the cation acetylcholine+; for SNP (Roche Products Ltd., Welwyn Garden City, UK) cathodal currents were employed to transfer the anion NP-.

As the solutions are unstable with time, the drugs were dissolved on the day of the test in sterile deionised water for SNP and in mannitol (inert vehicle) for acetylcholine to produce a 1% solution. Doses of acetylcholine and SNP were calculated from the dose-responses curves published by Westerman et al.(**1988**) with the aim to evaluate the maximum vasodilatatory response without inducing an axon reflex.

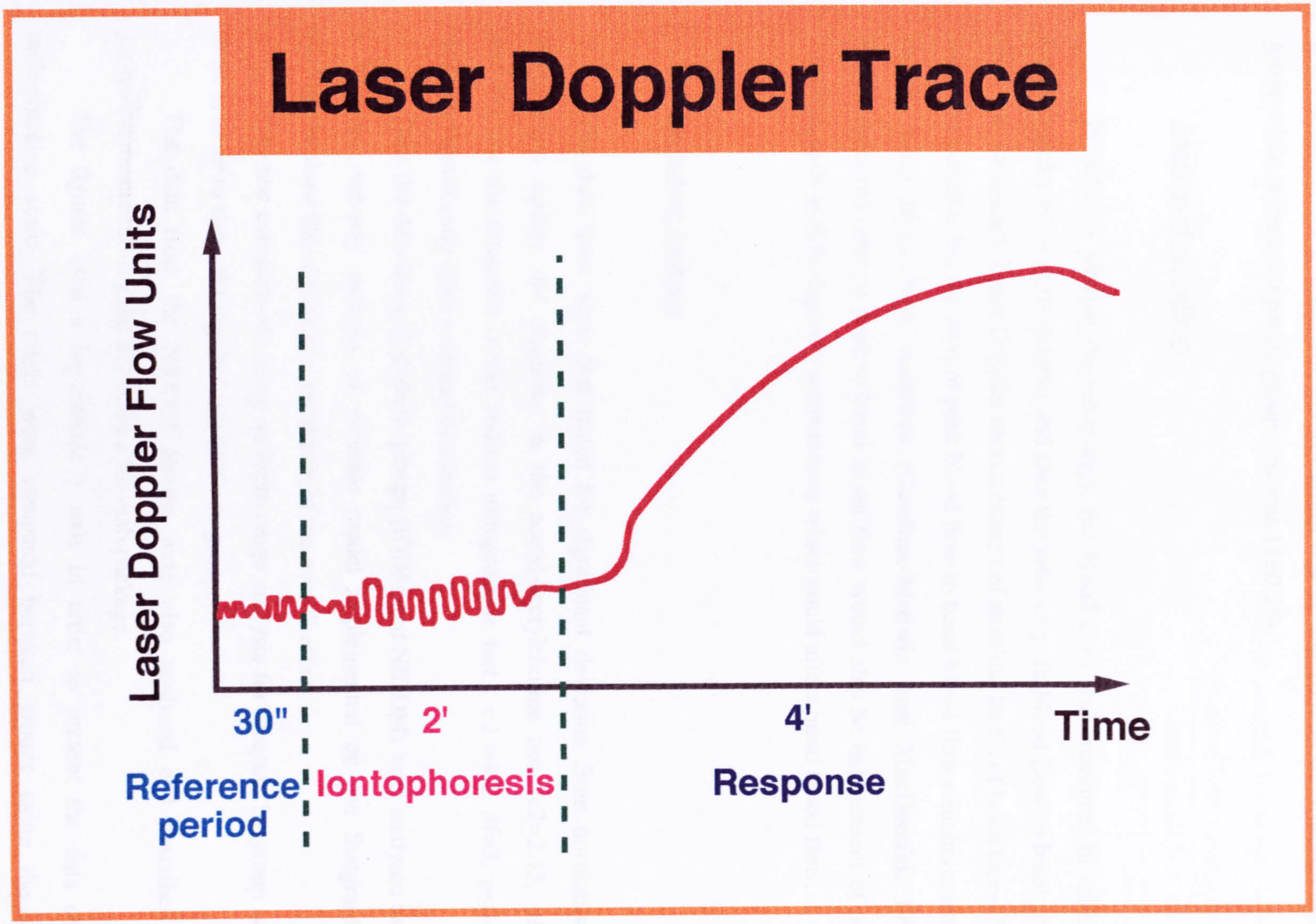
Therefore considering that the vasodilatatory response is dependent on the intensity of the electric current (100μA) and the time of exposure (2 minutes) to this current, a total charge of 12 mC was applied. At this low intensity, the current was either imperceptible or a very faint sensation of tingling was reported by the patients. If higher currents are employed, local electrically induced axon reflex vasodilatation could be induced.

The application of each drug was given at a different site on the dorsum of the foot to avoid interference with any previous vasodilatation.

The Laser Doppler blood flow measurements were done using a linear scale **(Nitzan et al., 1988; Ahn et al., 1987)** and the Moor LD flowmeter settings comprised of a recording bandwidth of 14.9Hz and a time constant of 0.5 seconds.

At the beginning of the test, basal blood flow was measured for 30 seconds; then iontophoresis was performed for 2 minutes and then the vasodilatatory responses were measured for 4 minutes, long enough to allow the recording of the peak blood flow (Fig. 7.8.1).

Fig. 7.8.1 Laser Doppler blood flow measurements



Reproducibility of the laser Doppler measurement

Laser Doppler measurements had a coefficient of variation of 45±21.2% (Mean±SD) in the non-diabetic control group and of 38±6.6% in the diabetic control group while in the neuropathic group, this was 11±0.2%.

Analysis of recordings

In order to analyse the recordings, the blood flow was measured in arbitrary Laser Doppler Flow units (LDFu) and then the ratio of peak blood flow to basal blood flow was calculated. Laser Doppler measurements of absolute levels of basal blood flow might be variable, but the ratio of peak blood flow to basal blood flow remains constant, despite basal blood flow variations (**Gardner-Medwin and MacDonald, 1995**). Furthermore the ratio of peak to basal blood flow would also be independent of other variables such as differing skin temperatures which could affect basal blood flow.

Statistical Analysis

The data from were first tested for significant deviation from normality of distribution: neither the measures in the acetyl-acetylcholine test ($c2=2.45$, $df=3$, $p<0.48$) nor the measures in the sodium nitroprusside test ($c2 =4.2$, $df=3$, $p<0.24$) differed significantly from a normal distribution.

Then the data from all diabetic groups (IDDM and NIDDM) were analysed using a standard one-way analysis of variance model implemented on the Statgraphics package to show the statistical significance of the overall effect.

Post-hoc comparisons using multiple range analysis for measure by group were done in order to show the significance between groups.

The data from the NIDDM groups were also analysed and described as geometric mean±anti-logged SD using a Minitab package.

The figures used a logarithmic y axis in order to present the data on a multiplicative scale. The ratios were compared between groups using the log-transformed values and t-test was done in order to show the significance between groups.

7.8.4 Results

The basal blood flow values, before iontophoresis was performed, were not found to be statistically significantly different in the three groups in the study, whether they included all diabetic (IDDM and NIDDM) patients or only the NIDDM patients versus the control subjects.

Table 7.8.3 Basal blood flow and vasodilatatory responses to acetylcholine and SNP iontophoresis in NIDDM patients with and without neuropathy compared to non-diabetic controls and expressed as geometric mean±anti-logged SD.

	Basal blood flow (LDFu)	**Acetylcholine** Ratio	**Sodium nitroprusside** Ratio
Controls (n=10)	14.01±1.71	9.81±1.65	7.02±2.05
Diabetic controls (n=7)	12.55±1.69 (p=0.67, NS)	3.49±1.67 (p<0.005)	6.42±1.56 (p=0.75,NS)
Neuropathic patients (n=8)	10.91±1.59 (p=0.30, NS)	3.50±2.03 (p<0.005)	2.10±2.0 (p<0.005)

Geometric mean±anti-logged SD

The values of the difference between basal blood flow and peak blood flow after iontophoresis of acetylcholine were also expressed as mean±SEM as seen in Table 7.8.4

Table 7.8.4 Vasodilatatory responses to acetylcholine and sodium nitroprusside iontophoresis in all neuropathic and non-neuropathic diabetic patients compared to controls and expressed as Mean±SEM.

	Acetylcholine		**Sodium nitroprusside**	
	LDFu	Ratio	LDFu	Ratio
Controls (n=10)	109.7±18.9	10.9±1.8	68.1±8.7	8.5±1.6
Diabetic controls (n=10)	67.0±9.4 (p<0.05)	5.8±1.1 (p<0.05)	70.8±16.4 (NS)	9.2±2.4 (NS)
Neuropathic patients (n=10)	29.6±9.8 (p<0.01)	4.1±0.7 (p<0.01)	15.5±6.8 (p<0.01)	2.8±0.7 (p<0.01)

Mean±SEM LDFu = Laser Doppler Flow units

<u>Vasodilatatory responses to acetylcholine iontophoresis</u>

Compared to non-diabetic control subjects, who showed a considerable increase in their blood flow (109.7±18.9 LDFu), all the diabetic groups showed a significantly reduced vasodilatatory response: diabetic controls (67.0±9.4 LDFu, $p<0.05$) and neuropathic patients (29.6±9.8 LDFu, $p<0.01$).

Although some of the neuropathic patients had no response at all to acetylcholine iontophoresis (Figure 7.8.2), there was no significant difference between the neuropathic group and the diabetic control group ($p=0.9$).

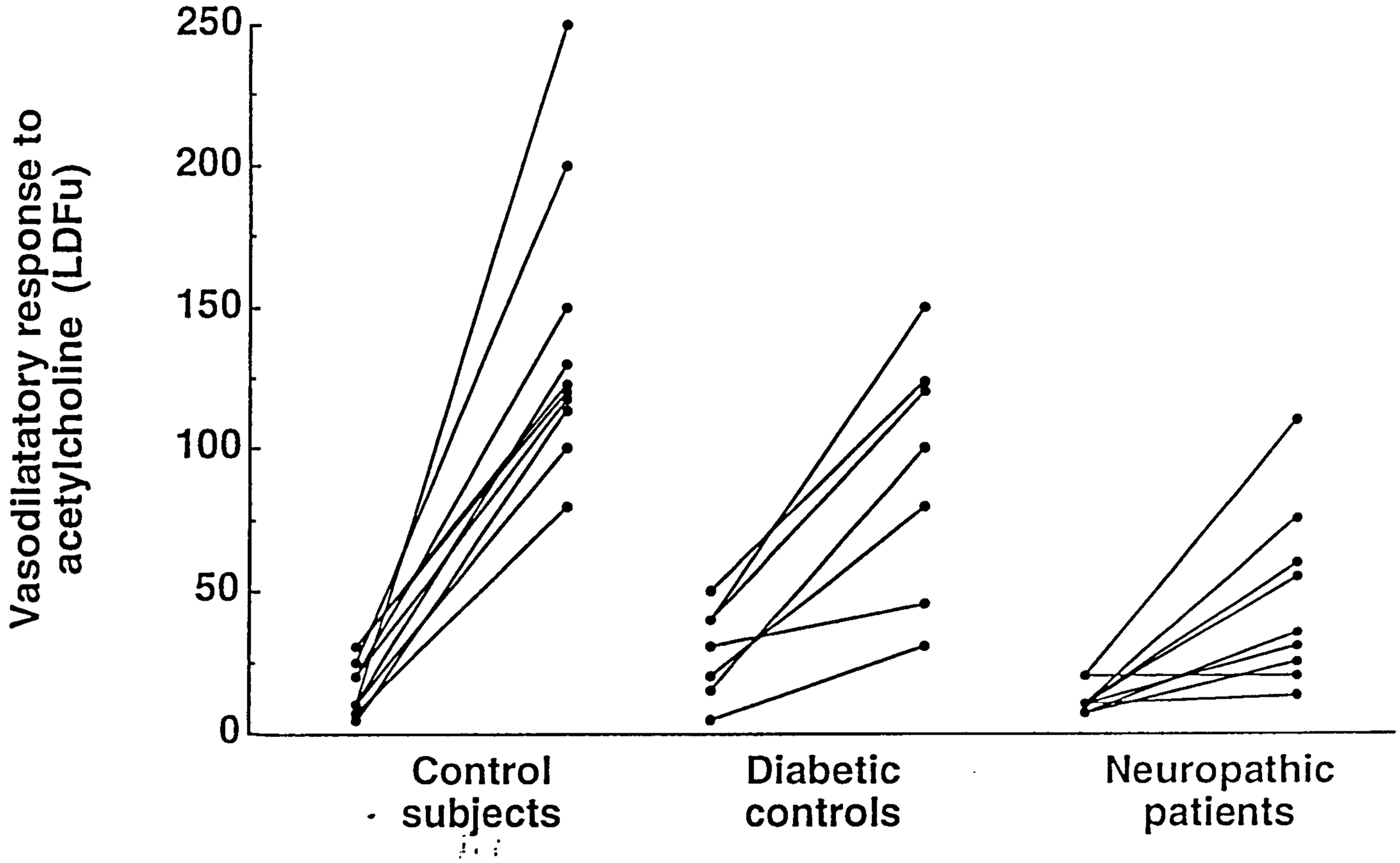


Fig. 7.8.2 Laser Doppler measurements of vasodilatatory responses to acetylcholine iontophoresis in neuropathic patients versus diabetic and non-diabetic controls

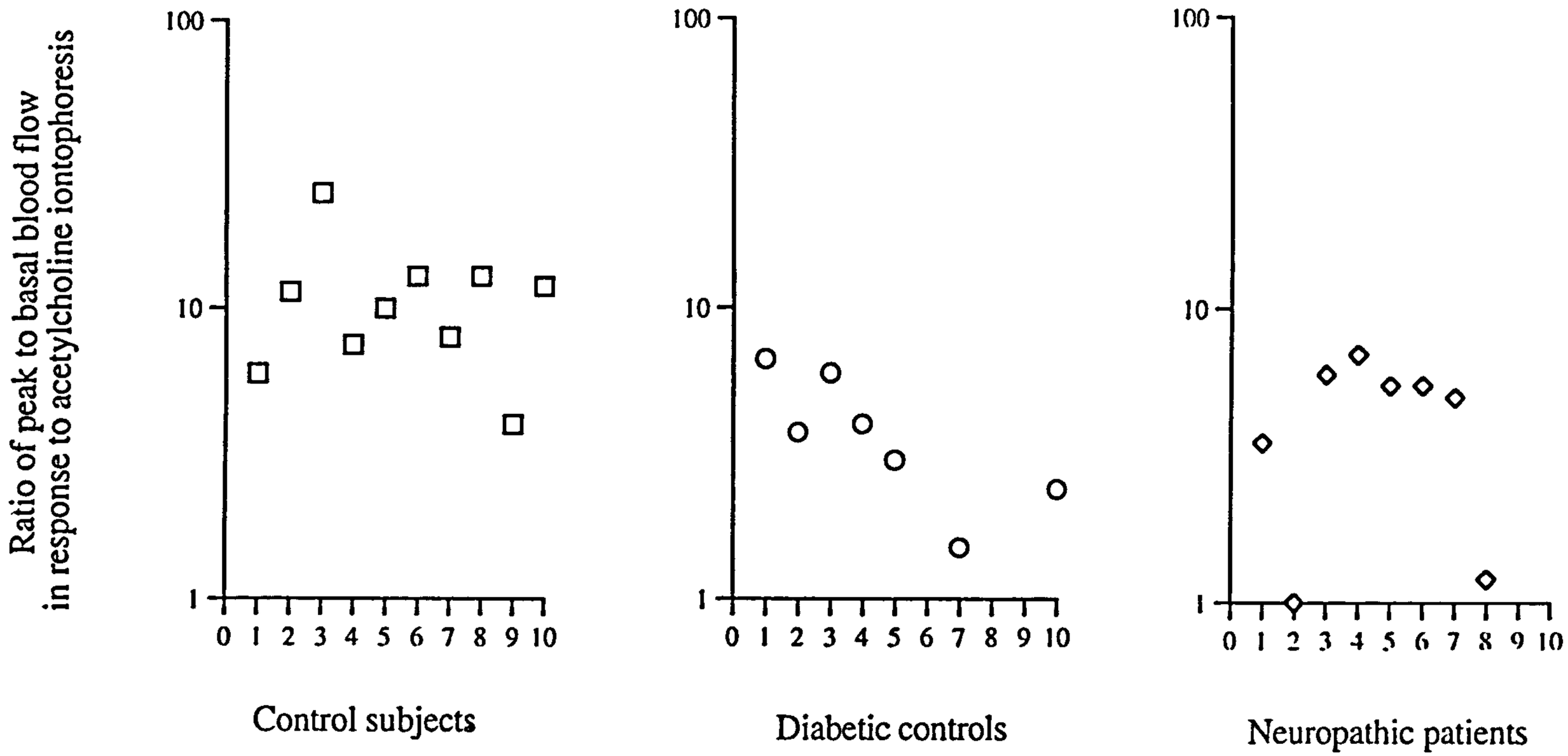


Fig. 7.8.3 Ratio between the peak blood flow after, and basal blood flow before acetylcholine iontophoresis in neuropathic patients versus diabetic and non-diabetic controls

The ratio of blood flow increase versus the basal blood flow (Table 7.8.4) also showed that both the IDDM and NIDDM controls (ratio=5.8±1.1, $p<0.05$) and the diabetic (IDDM and NIDDM) neuropathic patients (ratio=4.1±0.7, $p<0.01$) had a significant decrease in their endothelial vasodilatatory response to acetylcholine versus non-diabetic subjects (ratio=10.9±1.8).

When the geometric mean of the ratio was calculated in the NIDDM patients, similar results became apparent (Table 7.8.3). All the NIDDM groups showed a significantly reduced (Fig. 7.8.3) vasodilatatory response: diabetic controls (ratio= 3.49±1.67, $p<0.005$) and neuropathic patients (ratio=3.50±2.03, $p<0.005$) when compared to non-diabetic control subjects (ratio=9.81±1.65).

<u>Vasodilatatory responses to sodium nitroprusside iontophoresis</u>

The blood flow increase in response to the iontophoresis of SNP was assessed in the three groups (Fig. 7.8.4): the neuropathic patients, the diabetic control patients without neuropathy and the non-diabetic control subjects.

Compared to non-diabetic control subjects who showed a good vasodilatatory response (68.1±8.7 LDFu), the neuropathic group including IDDM and NIDDM patients was the only group which had a reduction in their vasodilatation (15.5±6.9 LDFu, $p<0.01$). The diabetic (IDDM and NIDDM) control group showed a similar vasodilatation (70.8±16.4 LDFu) when compared to non-diabetic controls (68.1±8.7 LDFu).

There was also a significant reduction in vasodilatation in the diabetic (IDDM and NIDDM) neuropathic patients (15.5±6.9 LDFu) when compared to the diabetic (IDDM and NIDDM) controls (68.1±8.7 LDFu, $p<0.01$).

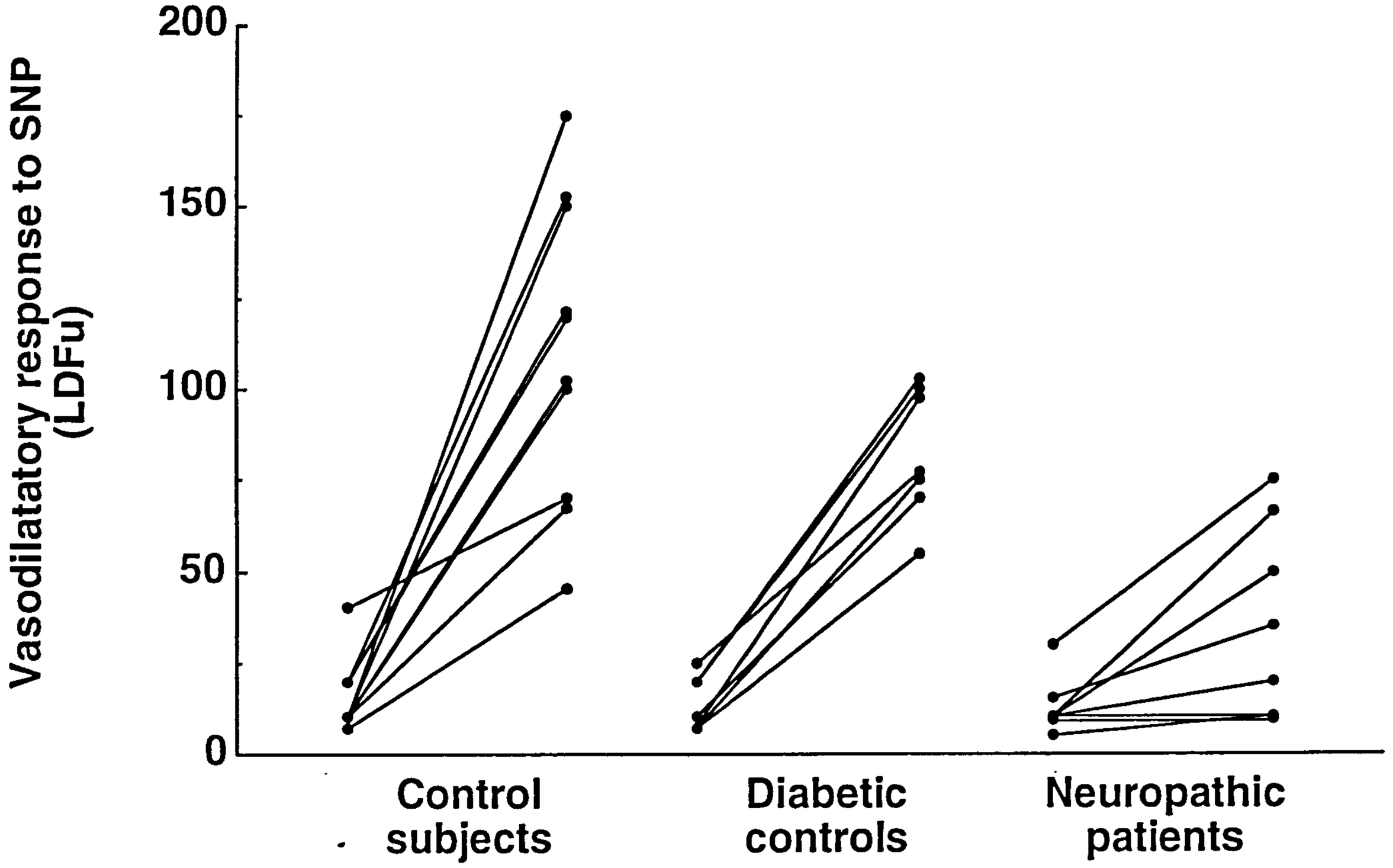


Fig. 7.8.4 Laser Doppler measurements of vasodilatatory responses to sodium nitroprusside iontophoresis in neuropathic patients versus diabetic and non-diabetic controls

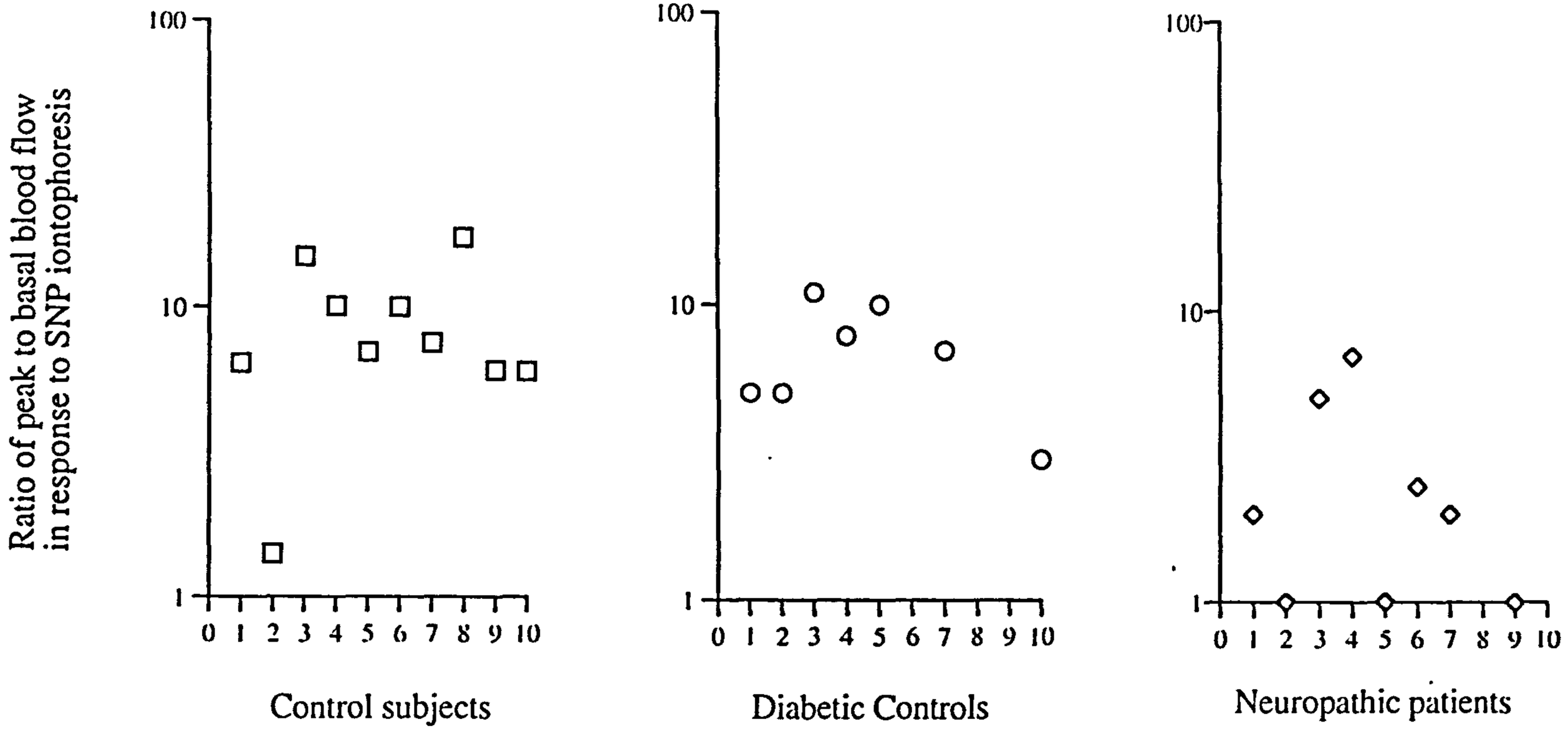


Fig. 7.8.5 Ratio between the peak blood flow after, and basal blood flow before sodium nitroprusside iontophoresis in neuropathic patients versus diabetic and non-diabetic controls

When the ratio between the peak blood flow after iontophoresis and the basal blood flow before iontophoresis was calculated as Mean±SEM (Table 7.8.4), again the only group which had a significant reduction in their ability to vasodilate to SNP was the diabetic (IDDM and NIDDM) neuropathic group.

Similarly when the geometric mean and the anti-logged SD (Table 7.8.3) were calculated in the NIDDM only groups, the neuropathic NIDDM patients showed a significant decrease (Fig. 7.8.5) in the smooth muscle ability to produce vasodilatation in response to SNP (ratio=2.10±2.0, $p<0.005$) when compared to both non-diabetic control subjects (ratio=7.02±2.05) and the NIDDM diabetic control group (ratio=6.42±1.56, $p=0.75$).

<u>Comparison of the vasodilatatory responses to acetylcholine and to SNP iontophoresis in the neuropathic group</u>

When the responses to the two agents were compared in the neuropathic patients (Figure 7.8.6), the response to SNP in the same individual was always smaller than the response to acetylcholine.

The results found in the NIDDM subgroups were not statistically different from the results found in the all diabetic (IDDM and NIDDM) groups.

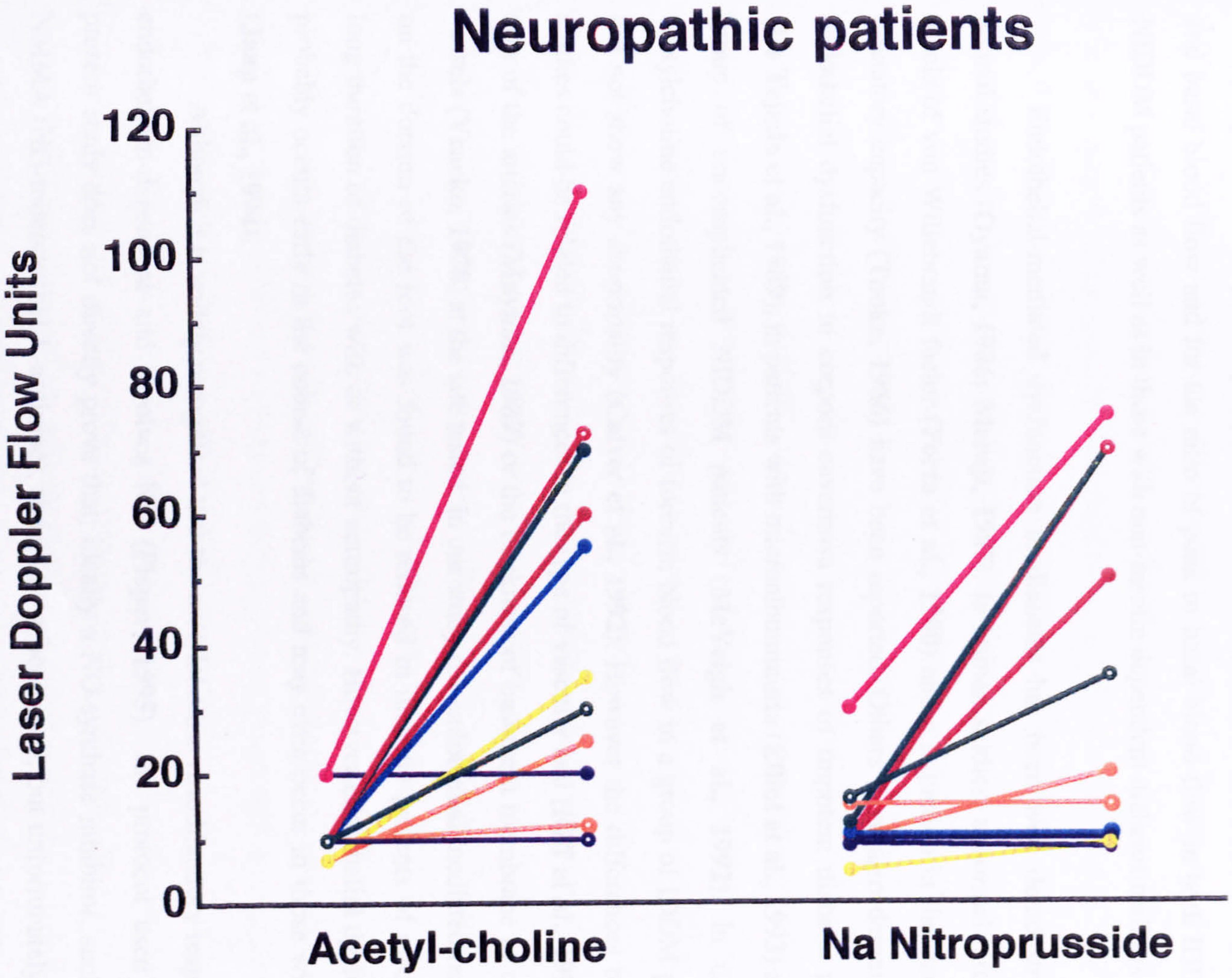


Fig. 7.8.6 Comparison of vasodilatatory responses to acetylcholine and sodium nitroprusside iontophoresis in the neuropathic group

7.8.5 Discussion

This study shows that acetylcholine induced endothelium dependent vasodilatation in the foot was impaired in all the diabetic patients whereas the smooth muscle response to sodium nitroprusside was severely blunted only in diabetic patients with peripheral sensory neuropathy. This was true for both the difference between peak and basal blood flow and for the ratio of peak to basal blood flow in both IDDM and NIDDM patients as well as in those with non-insulin dependent diabetes mellitus only.

Endothelial-mediated dysfunction in diabetes has been well demonstrated in animal studies (**Oyama, 1986; Meraji, 1987**). In human studies, abnormal circulating levels of von Willebrandt factor (**Porta et al., 1990**) and a reduction in the maximum dilatatory capacity (**Tooke, 1986**) have been reported. Others have also demonstrated endothelial dysfunction in corpora cavernosa responses of impotent diabetic patients (**De Tejada et al., 1989**), in patients with microalbuminuria (**Elliot et al., 1993**) and in a group of uncomplicated NIDDM patients (**McVeigh et al., 1992**). In contrast, acetylcholine endothelial responses of forearm blood flow in a group of IDDM patients did not show any abnormality (**Calver et al., 1992**). However the differences between studies could be related to differences in the type of vascular bed (**Kiff et al., 1991**), the size of the arteries (**Mayhan, 1989**) or the thickness of basement membrane of the skin vessels (**Vracko, 1970**) at the site tested. In our study the endothelial mediated reactivity on the dorsum of the foot was found to be reduced in diabetic patients of medium to long duration of diabetes with or without neuropathy. However endothelial dysfunction probably occurs early in the course of diabetes and may even occur in those with IGT (**Jaap et al., 1994**).

Although it is widely recognised that the acetylcholine vasodilatatory response is endothelium-dependent and involves NO (**Pieper, 1995**) the protocol used in the present study does not directly prove that; ideally a NO-synthase inhibitor, such as L-NMMA (NG-monomethyl-L-arginine), should have been used, but unfortunately this is not iontophoresable.

Endothelial responses may be affected by blood glucose levels as shown in animal studies (**Tesfamariam et al., 1991**). It is possible that NO produced by the endothelium may be quenched by glycation end products deposited in the subendothelial space (**Bucala et al., 1991**). However in animals this only occurs during very high blood

glucose levels constantly maintained over a week (**Lash, 1991**), which would be unusual in diabetic patients. Furthermore in humans, sustained moderate hyperglycaemia (blood glucose 10-15 mmol) does not affect these responses (**Houben et al., 1994**) and levels of HbA1c do not correlate with vascular reactivity (**McVeigh, 1992**). Nevertheless, both basal plasma glucose and HbA1c levels were comparable in all groups of diabetic patients and it is therefore unlikely that the differences in vascular responses in our study were influenced by diabetic control.

A diminished response to SNP was found only in the neuropathic group indicating that reduced endothelium-independent vasodilatation (vascular smooth muscle sensitivity to NO) is associated with neuropathy. However this association might also reflect either a more advanced state of the disease or less well controlled diabetes, with subsequent accumulation of advanced glycation end-products which leads to NO quench (**Bucala et al., 1991**). In uncomplicated IDDM, vasodilatation in response to SNP was found to be normal or minimally impaired in (**Smits et al., 1993**). In NIDDM there have been two recent studies: the first, in a group of NIDDM patients (although not totally free of diabetic complications) showed a blunted response to glyceryl trinitrate, which shares a common pathway with NO (**McVeigh, 1992**). However in another study (**Morris et al., 1995**) a reduction in both the vasodilatatory responses to acetylcholine and SNP were found in a group of NIDDM patients, but the majority of patients in that group had one or more diabetic complications such as retinopathy, nephropathy and neuropathy. Therefore the association of NIDDM with a defect of the SNP vasodilatation might be related to the presence of these diabetic complications. In this study, our diabetic patients both with and without neuropathy were matched for other complications namely retinopathy and nephropathy. This makes our findings in the neuropathic group even more interesting suggesting that the dysfunction at the smooth muscle level might be associated specifically with neuropathy.

Previously there have been only few studies on diabetic patients with well documented neuropathy. In the foot, acetylcholine mediated endothelial response to noxious stimuli (induced by mechanical stroking of the skin) was decreased, but SNP reactivity was not tested (**Parkhouse and LeQuesne, 1988**) and in a further study a reduction in the neurogenic response to acetylcholine was also demonstrated in patients with a history of foot ulceration (**Walmsley et al., 1991**). In vitro studies of isolated corpora cavernosa, taken from impotent diabetic patients (but with no indication of

their peripheral neuropathy status) confirmed impairment of the acetylcholine responses, although SNP reactivity was normal **(De Tejada et al., 1989)**. However in experimental neuropathy a reduced vasoreactivity to nitric oxide has been described, with impairment of NOS activity and less NO production, together with an increased endothelin-1 effect **(Kihara et al., 1995)**.

The localisation of NO-synthase in the autonomic and peripheral nerves **(Bredt, 1990)** suggests furthermore that synthesis of NO occurs directly in neurone. Evidence for neuronal production of NO has been also demonstrated in neuroblastoma cells **(Gorsky et al., 1990)** and in cerebellar cells **(Garthwaite et al., 1988)**. Thus the neurogenic origin (as opposed to the endothelial origin) of NO is relevant to our findings: the reduction in SNP response may be related to depletion of NO as neurotransmitter in the perivascular nerves as a result of neuropathy.

In a previous study the neurogenic origin of a diffusible NO-like factor which may act as an inhibitory neurotransmitter, was demonstrated in penile corpus cavernosum smooth muscle **(Kim et al., 1991)**. A messenger similar to NO was also found to mediate the non-adrenergic non-cholinergic relaxation in anococcygeus muscle of rat and mouse **(Gibson et al., 1990)** and an NO-like factor was shown to be released by nerves in the canine ileocolonic junction **(Bult et al., 1990)**.

In the skin the role of NO in maintaining the basal dilator tone is recognised **(Coffman et al., 1994)**, but there is also evidence that small afferent nerve fibres in the skin depend on NO as an essential intermediate for the amplification of the CGRP-mediated vasodilatation **(Herbert and Holzer, 1994)**.

Although the cause of the reduced response of the smooth muscle to SNP in the diabetic neuropathic patients is not known, it may be that neuropathy decreases the neurogenic production of NO or increases the production of vasoconstrictor neuropeptides or simply the smooth muscle is less responsive. A decreased vascular reactivity to the local release of neuropeptides from the peripheral nerve fibres has been reported previously **(Boolell and Tooke, 1990)**.

Reduced exposure of smooth muscle to NO of both endothelial and neurogenic origin might initially be expected to lead to smooth muscle up-regulation and increased vascular responses, which would contrast with our findings in severe neuropathic patients. In the early, mild stages of neuropathy denervation sensitivity and increased vascular responses might occur. However, in the late stages of neuropathy, smooth muscle dysfunction might progress to an impaired ability to react to NO donors. A

similar process has been described in iontophoresis studies of sudomotor responses in diabetic patients: in mild neuropathy there was increased sudomotor reactivity after iontophoresis in contrast to severe neuropathy, which was characterised by reduced responses (**Kihara, 1993; Lang, 1995**).

In the present study, the neuropathic patients were selected by measuring the vibration perception threshold which assesses only large fibre damage accepted as an indicator of late stage neuropathy (**Said et al., 1983; Guy et al., 1985**). In future studies to elucidate the mechanisms which underlay our observations, a more detailed analysis of the early stages of nerve damage, characterised by small fibre and autonomic defects, will be needed.

When we compared the responses to both vasodilatatory agents in the neuropathic group, the response to SNP was always smaller. The explanation might be that the SNP does not penetrate the skin in the same degree as acetylcholine.

Another possible explanation would be that SNP has a more direct, targeted approach to the smooth muscle, whereas acetylcholine triggers a cascade of events including prostacyclin, bradykinin and NO pathways.

The perivascular nerves, the endothelium and the smooth muscle create a complex system in which vasodilator agents such as prostacyclin (PGI2), endothelium-derived hyperpolarizing factor (EDHP) and NO counteract vasoconstrictor factors such as endothelin, angiotensin 2, thromboxan 2 and oxygen derived free radicals. Furthermore, there are neurotransmitters such as noradrenaline, neuropeptide Y and ATP which have a relaxing and/or contracting effect on the vasculature, according to the type of receptors to which they bind.

This highlights the need for further studies which ought to explore these different pathways using other vasodilator or vasoconstrictor neurotransmitters, in order to establish more precisely the site where neuropathy affects this complex system.

<u>Conclusion</u>

We have found that vascular endothelial responses are blunted in non-insulin dependent diabetes, while neuropathy might affect specifically the NO dependent smooth muscle reactivity. Future studies are needed to elucidate the underlying mechanisms of these observations.

7.9 Endothelium-dependent and endothelium-independent responses in non-diabetic patients with peripheral unilateral neuropathy

7.9.1 Introduction

The diabetic neuropathic foot suffers frequent ulceration, which is slow to heal, and is typically associated with abundant callus formation (**Edmonds et al., 1986**). Since neuropathic ulceration is often found in the presence of "bounding" pedal pulses, it has been suggested that there might be a specific diabetic "microangiopathy" which may be an important factor in ulceration by causing skin ischaemia (**Ward, 1982**).

Peak skin blood flow in response to thermal stimuli when measured from the dorsum of the foot has been shown to be reduced in diabetic patients without evidence of neuropathy (**Rayman et al., 1986**).

This has been interpreted as evidence of a diabetic microangiopathy, although the possibility of some degree of vascular denervation can not be excluded. Blood flow and its neurogenic control in the diabetic neuropathic foot is known to be abnormal: there is excess arteriovenous shunt flow due to a reduced sympathetic tone (**Watkins 1983**; **Edmonds et al, 1982; Boulton, 1982**), and this flow is also controlled by local reflexes, whose function may be altered in diabetic neuropathy (**Rayman, 1986**). Indeed it has been suggested that Charcot arthropathy may result primarily from loss of vascular control which may result in exaggerated inflammatory vascular responses to trauma. This may result in bony reabsorption and precipitate fractures.

Also in the previous subchapter we have demonstrated that in the presence of neuropathy specifically, neurovascular reactivity is decreased in response to iontophoresis of SNP. Thus local neurogenic control may be of primary importance in the development of complications of the neuropathic limb, rather than a specific diabetic microangiopathy.

7.9.2 Aim of study

To assess the effect of nerve damage per se on vascular reactivity in non-diabetic patients and to ascertain whether neuropathy in the absence of diabetes, which might introduce a specific microangiopathy, could reproduce the skin blood flow abnormalities which we had previously demonstrated in the diabetic neuropathic foot. The microvascular reactivity to SNP and acetylcholine iontophoresis in non-diabetic subjects with a predominantly unilateral neuropathy and foot ulceration was assessed. The contralateral limb served as the control in these patients.

7.9.3 Methods

Neuropathy assessment

The presence of nerve damage was assessed in both lower limbs by clinical examination of the ankle reflexes and foot pulses, together with recording the vibration sensory threshold (VPT). Thermal sensory thresholds (TPT) were also recorded with a Thermal tester (Somedic, Stockholm, Sweden) from the dorsum of the foot and the response to five warm and five cold stimuli delivered at random time intervals was recorded (normal range 1-5°C).

The temperature of the skin was also measured on the dorsum of the both feet using the thermocouple attached to the Laser Doppler probe.

Iontophoresis and Laser Doppler flowmetry

Iontophoresis of acetylcholine and SNP and skin blood flow measurements were done using a Moor Laser Doppler flowmeter and iontophoresis device (Moor Instruments Ltd., Axminster, UK), which were described in the previous subchapter.

The protocol for skin blood flow measurement

As before, the changes in skin blood flow in response to iontophoresis were assessed with a Moor Laser Doppler. A probe of the Laser Doppler was attached to a plastic chamber placed on the dorsum of the "neuropathic" foot and the other probe was

similarly placed on the unaffected foot which acted as a control. The dorsum of the foot was also chosen as the testing site in these patients as those described in the previous subchapter. The study conditions were similar and the iontophoresis and Laser Doppler techniques were used as described in the previous subchapter.

Vasodilatatory responses were compared between 'neuropathic' limbs and 'control' limbs. One patient had undergone major amputation of the contralateral leg and thus it was not possible to carry out control measurements. Finally vasodilatatory responses from the 'neuropathic' limbs were compared to those obtained from neuropathic patients in the previous subchapter, and respectively responses from 'control' limbs were compared to responses from non-diabetic control subjects in the previous subchapter.

7.9.4 Patients

There were 5 patients with neuropathy due to tumour or of traumatic origin which induced predominantly unilateral nerve damage and foot ulceration. Their microvascular reactivity to iontophoresis of acetylcholine and SNP was assessed.

Table 7.9.1 Clinical details of non-diabetic patients with unilateral nerve damage

Patients	Age (yrs.)	Sex	Aetiology of nerve damage
1. T.Q.	21	F	tumour at L5 - S1 level
2. D.T.	27	M	gun shot wound in the groin in '88
3. A.M.	63	F	hereditary sensory neuropathy
4. P.P.	42	M	gun shot wound in L leg in '75
5. J.G.	65	M	spina bifida

The patients included in the study were free from major peripheral arterial disease: foot pulses were easily palpable and ankle:brachial ratios were > 1. None were on vasoactive drugs at the time of their assessment. None of the subjects had peripheral oedema. Individual neurophysiological characteristics in control limbs versus neuropathic limbs in non-diabetic patients are shown in Table 7.9.2

Table 7.9.2 Individual neurophysiological characteristics in control limbs versus neuropathic limbs in non-diabetic patients

	Patient 1 (T.Q.)		Patient 2 (A.M.)		Patient 3 (J.G.)		Patient 4 (P.L.)		Patient 5 (D.T.)	
	Control foot	Neuropathic foot	Control foot	'Neuropathic' foot	Control foot	'Neuropathic' foot	Control foot	'Neuropathic' foot	Control foot	'Neuropathic' foot
			amputated							
Vasodilatatory response to **Acetylcholine (LDFu)**	35	5		15	10	0.5	10	0.7	30	0.2
Ratio (Peak/Basal flow)	8	7		1.4	2	1	1	1	4	1
Vasodilatatory response to **Sodium nitroprusside (LDFu)**	27	5		10	15	7	100	116	70	17
Ratio (Peak/Basal flow)	5	2		1.5	1.7	1.2	11	30	3	2
Vibration perception threshold (VPT)	30	40		35	25	50	18	50	5	27
Hot thermal perception threshold (TPT for hot°C)	3.1	15		15	4.2	6.2	5.5	15	6.3	15
Cold thermal perception threshold (TPT for cold°C)	2.2	15		3.6	4.2	4.9	1.3	15	3.6	15
Skin temperature (t°C)	33.6	32.5		33.3	32	31.8	28.5	26.7	33.7	32.8

Patient 1 (TQ)

This 21 year old woman was diagnosed as having a yolk sac tumour of the pelvis at the age of six. This resulted in damage to the sacral plexus and nerve roots L4 to S1. She developed weakness of dorsiflexion of the right toes and foot and an extensive sensory loss under the right foot. C.T. scan confirmed a soft tissue mass inferior to the coccyx extending from the sacral coccygeal junction to the ischia. Histology revealed an endodermal sinus tumour. Myelogram was normal. Chemotherapy was given, with resolution of the tumour mass, but the neurological deficit remained predominantly on the right limb.

Three years subsequently, she developed a paralytic equinovarus of the right foot with trophic neuropathic ulceration under the 5th metatarsal head. The ulceration healed, but was recurrent, and required regular chiropody to remove callus tissue. Her random blood glucose was 5.1 mmol/L.

Although the VPT was 40 volts in her right "neuropathic" foot, the VPT in the left "control" foot was also high (30 volts). However the TPTs for both hot and cold temperature were abnormal only in the right "neuropathic" foot. On the dorsum of the "neuropathic" foot the skin temperature was 32.5°C versus 33.6°C on the dorsum of the "control" foot.

Patient 2 (DT)

The neuropathy in this 27 year old man resulted from a deeply penetrating gun shot wound in the left groin, which resulted in damage to both the peroneal and tibial division of the left sciatic nerve. This resulted in weakness of both dorsiflexion and plantar flexion of the left foot an toes and sensory loss over the sole of the foot in the L5-S1 nerve root distribution.

The left foot became intermittently swollen over the following year, and the 2nd and 3rd toes became ulcerated with hyperkeratosis of the skin, and exuberant callus formation. The most persistent ulceration occurred however over the plantar phalangeal surface of the 1st toe, which has persisted for over 18 months. The random blood glucose was 4.9 mmol/L.

The VPT was increased (27 volts) only in his left "neuropathic" foot whereas his right "control" foot had a normal VPT (5 volts). In the "neuropathic" foot the TPT for both hot (15°C) and cold (15°C) temperature were abnormal. However in the "control" foot the TPT for hot temperature (6.3°C) and cold temperature (3.6°C) were moderately increased. On the dorsum of the "neuropathic" foot the skin temperature was 32.8°C and on the dorsum of the "control" foot, 33.7°C.

Patient 3 (AM)

This 63 year old lady developed a peripheral neuropathy of unknown aetiology 30 years previously, which resulted in a distal sensory loss of light touch, temperature and pain sensation over the lower legs and feet.

The plantar surface of the foot was particularly anaesthetic. This resulted initially in hyperkeratosis under the 1st metatarsal head of the left foot and subsequent ulceration which required a below knee amputation. The right foot also developed trophic ulceration under the 2nd to 4th metatarsal heads which necessitated a ray amputation of the 2nd toe. This required 6 months to heal and became recurrently ulcerated. This patient had a random blood glucose of 5.3 mmol/L.

The VPT in the remaining "neuropathic" foot was 35 volts. The TPT for hot temperature was 15, whereas the TPT for cold temperature was 3.6, nearly normal.

Patient 4 (PP)

A penetrating gun shot wound in the left upper thigh in 1975, during the Vietnam War, was the origin of a sciatic lesion in this 42 years old Vietnamese man. He had also a glancing bullet wound in the right leg. This resulted in weakness of both dorsiflexion and plantar flexion of the left foot and toes and sensory loss over the sole of the foot in the L5 nerve root distribution.

At his first appointment at the Diabetic Foot Clinic he presented with an ulceration of the heel and a history of foot ulceration. The random blood glucose was 4.8 mmol/L.

The VPT was much more raised (50 volts) in his left "neuropathic" foot than in his right "control" foot which had a moderately increased VPT (18 volts). Also in the

"neuropathic" foot the TPTs for hot(15°C) and cold (15°C) temperature were abnormal compared to the "control" foot where the TPT for hot temperature was moderately increased (5.5°C), whereas the TPT for cold temperature was normal (1.3°C). The "neuropathic" foot had a skin temperature of 26.7°C and the "control" foot had 28.5°C skin temperature.

Patient 5 (JG)

A lumbar myelomeningocele resulted in damage to the nerve roots L4, L5 and S1, innervating the right limb. This resulted in weakness of all movements of the right foot and an extensive sensory loss in this 65 year old man. This foot developed a talipes equinovarus deformity and subsequently became ulcerated on the prominent plantar surface of the mid foot.

The right foot has been recurrently ulcerated over the past 15 years, and has required regular chiropody to remove callus tissue. The random blood glucose was 5.0 mmol/L. VPT was 50 volts in his right "neuropathic" foot, but it was also slightly raised(25 volts) in his left "control" foot. However the TPTs for both hot and cold temperature were similar in both feet. Skin temperature on the dorsum of the "neuropathic" foot was 31.8°C versus 32°C on the dorsum of the "control" foot.

All patients gave their informed consent and the protocol was approved by the hospital ethical committee.

7.9.5 Results

In this study the foot with evidence of unilateral nerve damage was considered the neuropathic foot, as defined by significantly higher thresholds for vibration and thermal sensation, whereas the other foot was considered the control foot. The skin temperature was not significantly different between the neuropathic and the control limbs (Table 7.9.3).

Table 7.9.3 Neuropathy details of the 'control' limb versus the 'neuropathic' limb in non-diabetic patients with unilateral nerve damage

TEST	Control foot	Neuropathic foot	
VPT (V)	19.5 ± 5.4	40.4 ± 4.4	p<0.05
TPT+ (°C)	4.5 ± 0.5	13.2 ± 1.7	p<0.01
TPT- (°C)	2.8 ± 0.6	12.4 ± 2.5	p<0.005
Skin temperature (°C)	31.9 ± 1.2	30.9 ± 1.4	p = NS
Ankle reflexes	Present	Absent	-

VPT= vibration perception threshold

TPT+ = thermal perception threshold for hot

TPT- = thermal perception threshold for cold

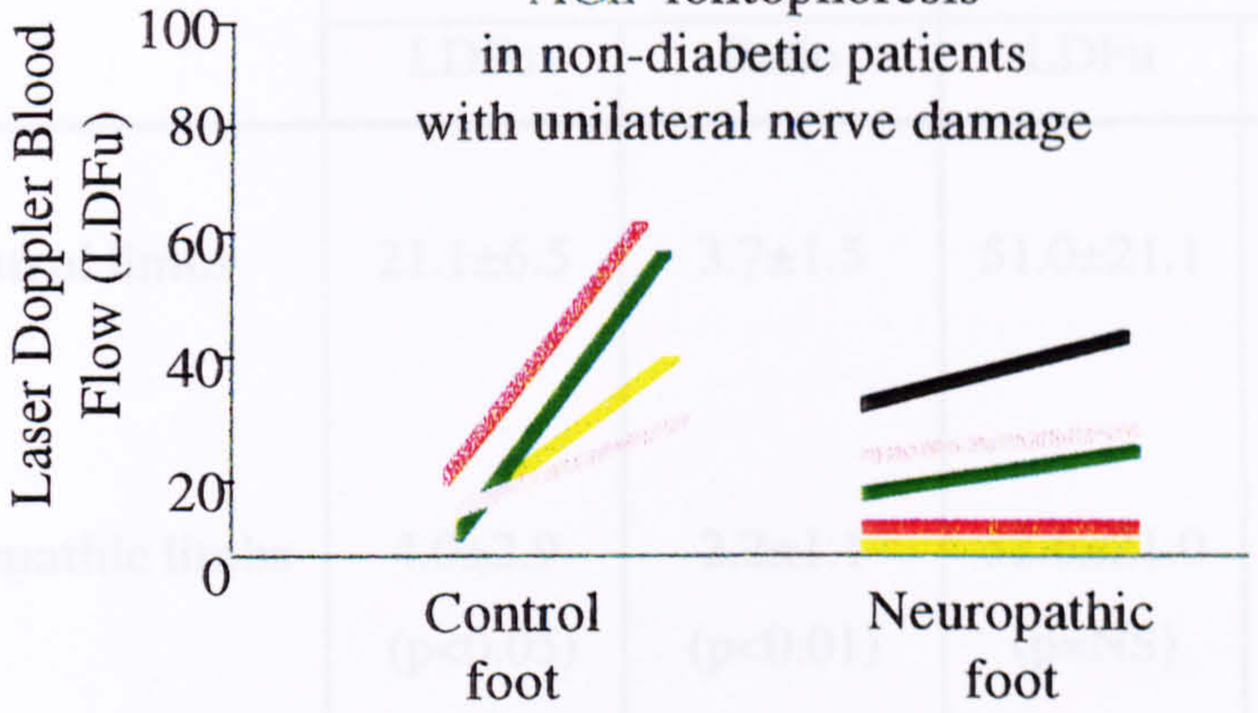
Vasodilatatory responses to acetylcholine iontophoresis

The values of the difference between basal blood flow and peak blood flow after iontophoresis of acetylcholine were expressed as mean±SEM.

Compared to the control feet, which showed an increase in the blood flow (21.1±6.5 LDFu), all the neuropathic feet showed a significantly reduced vasodilatatory response (4.0±2.9 LDFu, p<0.05) (Table 7.9.4), some of them had no response at all to acetylcholine iontophoresis (Figure 7.9.1).

When the ratio of peak blood flow to basal blood flow was calculated, again the neuropathic feet showed a significantly reduced vasodilatation to acetylcholine (2.2±1.1 versus 4.0±2.9, p<0.05 in controls).

Fig. 7.9.1 Vasodilatatory responses to ACh iontophoresis in non-diabetic patients with unilateral nerve damage



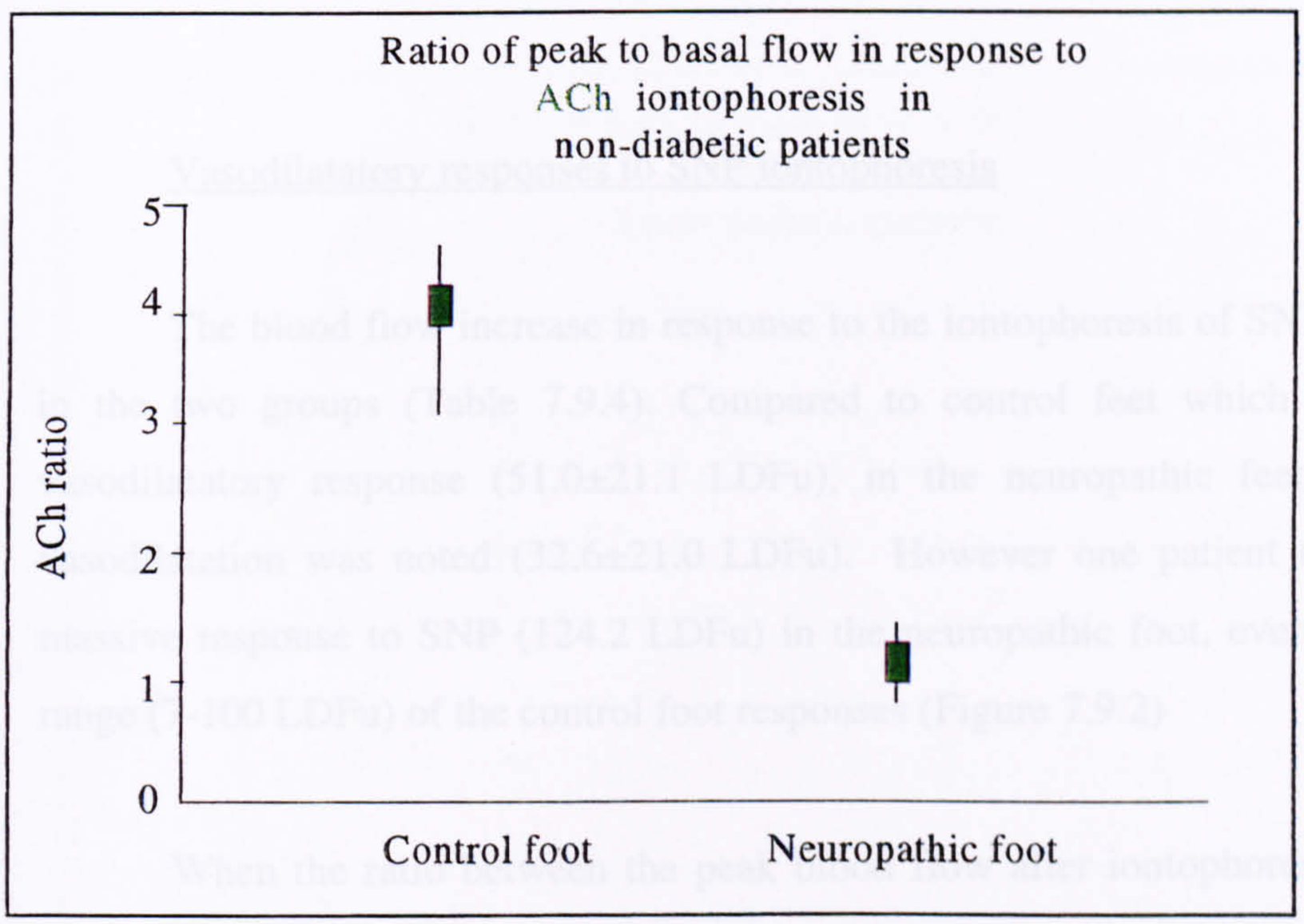


Table 7.9.4 Vasodilatatory responses to iontophoresis of acetylcholine and SNP in 'control' limbs versus 'neuropathic' limbs in non-diabetic patients

	Acetylcholine		Sodium nitroprusside	
	LDFu	Ratio	LDFu	Ratio
Control limbs	21.1±6.5	3.7±1.5	51.0±21.1	7.4±5.6
Neuropathic limbs	4.0±2.9 (p<0.05)	2.2±1.1 (p<0.01)	32.6±21.0 (p=NS)	5.0±2.1 (p=NS)

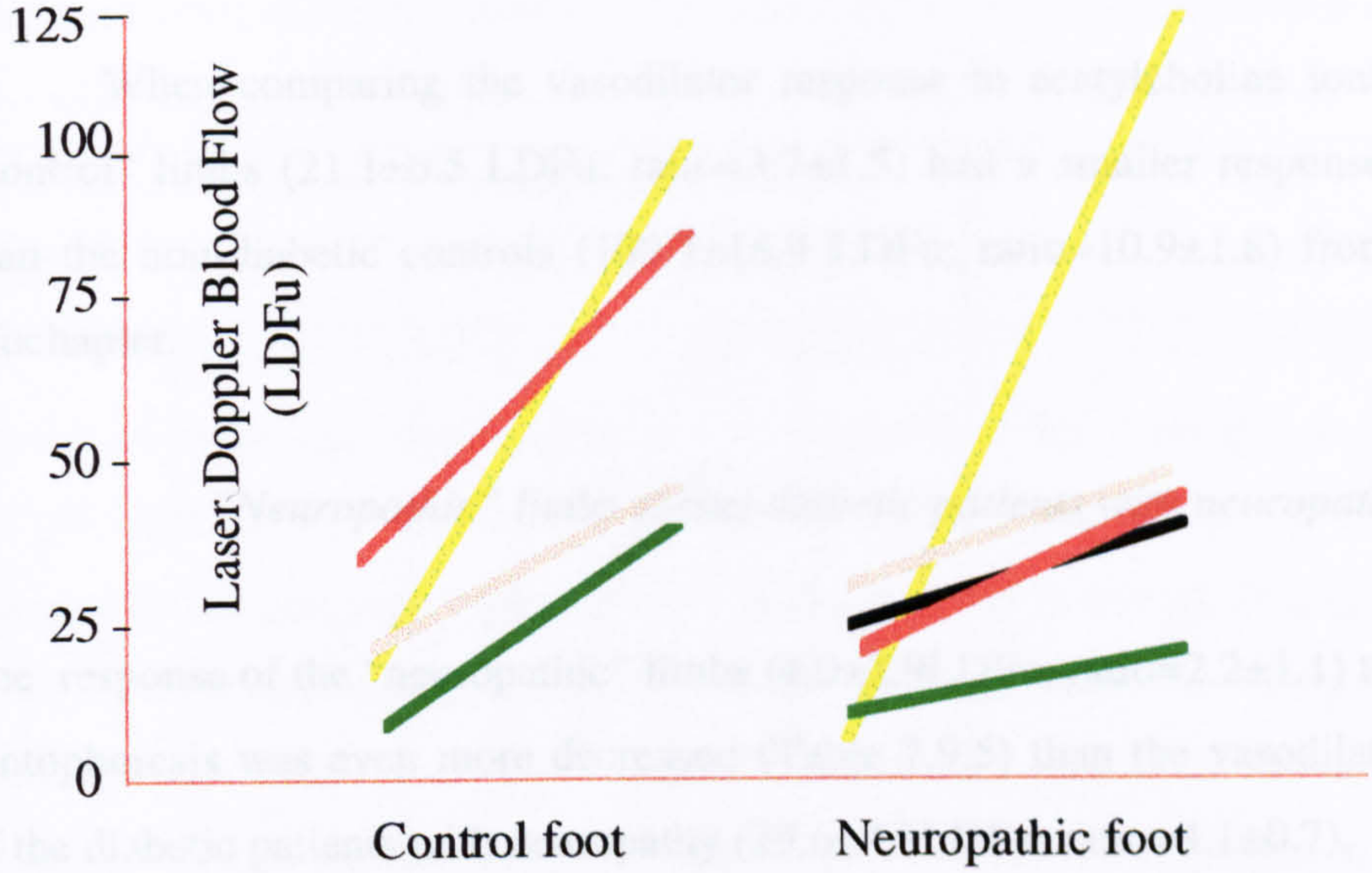
Mean±SEM LDFu = Laser Doppler Flow units

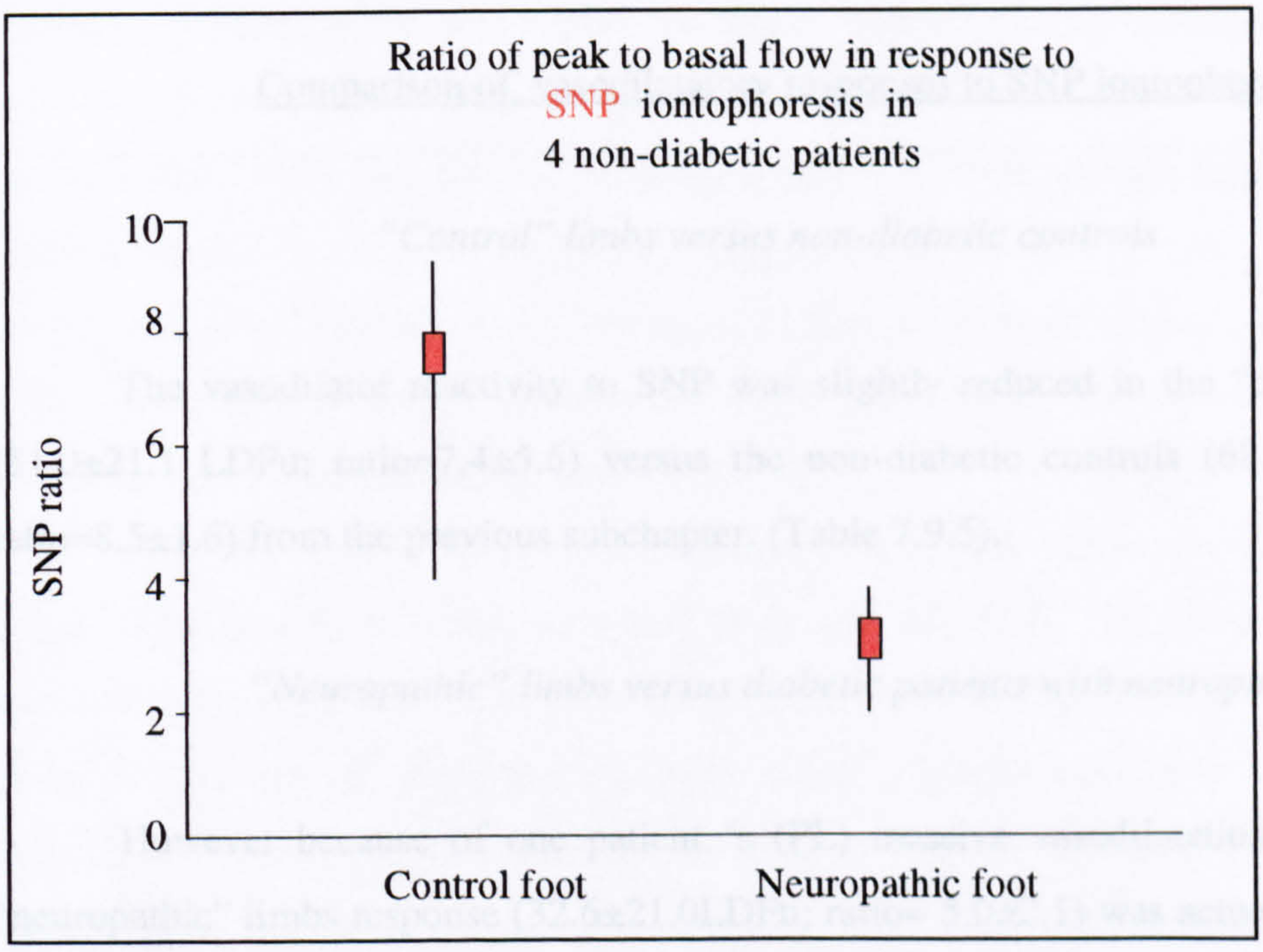
Vasodilatatory responses to SNP iontophoresis

The blood flow increase in response to the iontophoresis of SNP was calculated in the two groups (Table 7.9.4). Compared to control feet which showed a good vasodilatatory response (51.0±21.1 LDFu), in the neuropathic feet a reduction in vasodilatation was noted (32.6±21.0 LDFu). However one patient (PL) exhibited a massive response to SNP (124.2 LDFu) in the neuropathic foot, even higher than the range (7-100 LDFu) of the control foot responses (Figure 7.9.2)

When the ratio between the peak blood flow after iontophoresis and the basal blood flow before iontophoresis was calculated in the 5 patients, a reduced vasodilatation was found in 4 out of 5 patients in the neuropathic foot . However the difference between the control (7.4±5.6) and the neuropathic (5.0±2.1) groups did not reach statistical significance (Table 7.9.4) because of the excessive vasodilatation (ratio=30) demonstrated by one patient (PL) in the neuropathic foot.

Fig. 7.9.2 Vasodilatatory responses to SNP iontophoresis in non-diabetic patients with unilateral nerve damage





7.9.6 Comparisons with results from previous subchapter

Comparison of vasodilatatory responses to acetylcholine iontophoresis

"Control" limbs versus non-diabetic controls

When comparing the vasodilator response to acetylcholine iontophoresis, the "control" limbs (21.1±6.5 LDFu; ratio=3.7±1.5) had a smaller response (Table 7.9.5) than the non-diabetic controls (109.7±18.9 LDFu; ratio=10.9±1.8) from the previous subchapter.

"Neuropathic" limbs versus diabetic patients with neuropathy

The response of the "neuropathic" limbs (4.0±2.9LDFu; ratio=2.2±1.1) to acetylcholine iontophoresis was even more decreased (Table 7.9.5) than the vasodilatatory response of the diabetic patients with neuropathy (29.6±9.8LDFu; ratio=4.1±0.7).

Comparison of vasodilatatory responses to SNP iontophoresis

"Control" limbs versus non-diabetic controls

The vasodilator reactivity to SNP was slightly reduced in the "control" limbs (51.0±21.1 LDFu; ratio=7.4±5.6) versus the non-diabetic controls (68.1±8.7 LDFu; ratio=8.5±1.6) from the previous subchapter. (Table 7.9.5).

"Neuropathic" limbs versus diabetic patients with neuropathy

However because of one patient 's (PL) massive vasodilatation to SNP, the "neuropathic" limbs response (32.6±21.0LDFu; ratio= 5.0±2.1) was actually higher (Tb 7.9.5) than the reactivity of diabetic patients with neuropathy (15.5±6.8LDFu; ratio=2.8±0.7) from the previous subchapter.

Table 7.9.5 Comparisons of vasodilatatory responses to acetylcholine and sodium nitroprusside iontophoresis in neuropathic diabetic patients versus 'neuropathic' limbs in non-diabetic patients with peripheral unilateral neuropathy and control subjects versus 'control' limbs in non-diabetic patients with peripheral unilateral neuropathy

	Acetylcholine		Sodium nitroprusside	
	LDFu	Ratio	LDFu	Ratio
Control subjects	109.7±18.9	10.9±1.8	68.1±8.7	8.5±1.6
Control limbs	21.1±6.5	3.7±1.5	51.0±21.1	7.4±5.6
Neuropathic patients (n=10)	29.6±9.8 (p<0.01)	4.1±0.7 (p<0.01)	15.5±6.8 (p<0.01)	2.8±0.7 (p<0.01)
Neuropathic limbs	4.0±2.9	2.2±1.1	32.6±21.0	5.0±2.1

Mean±SEM

LDFu = Laser Doppler Flow units

7.9.7 Discussion

In the previous chapter it has been reported that diabetic patients with neuropathy have a reduction in their vasodilatation to acetylcholine and specifically to SNP. This decrease in response was also found in 4 out of 5 patients with unilateral neuropathy we studied. However one patient developed a massive response to SNP iontophoresis in the predominantly neuropathic foot. It is difficult to explain it although it may be related to denervation hypersensitivity.

Since perivascular nerves are separated from endothelial cells by vascular smooth muscle, it is possible that there are functional and trophic interactions between the perivascular nerves, smooth muscle and endothelial cells. Close apposition of perivascular nerves varicosities to the endothelium has been demonstrated. Furthermore it has been strongly suggested that neuropeptides play a role in neurochemical control of vascular reactivity and in cell differentiation, proliferation, hypertrophy and regeneration (**Burnstock, 1993**).

Studies regarding the neurotransmitters involved in the dynamics of the vasculature have clearly proven the role of NO released from the vasodilator nerves in producing arterial smooth muscle vasodilatation (**Toda et al., 1993**). Furthermore an ultrastructural study has demonstrated the presence of NOS in both the axons and the endothelial cells throughout the cell cytoplasm and in association with membranes of mitochondria, endoplasmic reticulum and cytoplasmic/synaptic vesicles suggesting that both perivascular nerves and endothelial cells may be involved in vasomotor control of microcirculation (**Loesch et al., 1994**).

Reduced exposure of smooth muscle to NO of both endothelial and neurogenic origin might initially be expected to lead to smooth muscle up-regulation and increased vascular responses, which would contrast with our findings in severe neuropathic patients. Although a study looking at the effect of denervation on bronchial smooth muscle has also found that denervation reduced smooth muscle ability to contract (**McLarty et al., 1993**). However in the early, mild stages of neuropathy denervation sensitivity and increased vascular responses might occur. In contrast, in the late stages of neuropathy, smooth muscle dysfunction might progress to an impaired ability to react to NO donors. A similar process has been described in iontophoresis studies of sudomotor responses in diabetic patients: in mild neuropathy there was increased

sudomotor reactivity after iontophoresis in contrast to severe neuropathy, which was characterised by reduced responses (**Kihara et al.,1993**). Furthermore another study which induced autonomic neuropathy in the rat perivascular nerves, found a graded destruction of nerve types: CGRP-immunoreactive nerves greater than NA(noradrenaline)-immunoreactive nerves greater than substance P-imunoreactive nerves suggestive of a differential sensitivity of different nerve types (**Ralevic et al., 1991**).

The importance of the perivascular innervation in lesions of the arterial wall is highlighted by an ultrastructural study showing that in regions of the carotid artery where intimal thickening occurred there was an associated degeneration of the perivascular nerve network (**Scott et al., 1992**). It is recognised that sympathetic nerves can also exert a trophic influence (**Bevan et al., 1979**) on the structure and function of the smooth muscle (**Scott et al., 1995**). Furthermore the presence of sympathetic nerve fibres in association with single isolated smooth muscle cells appears to prevent their phenotypic modulation to a synthetic state: this trophic influence was demonstrated to be dependent upon a substance present within the nerve. (**Chamley et al., 1976**). However the role of both the sympathetic and peptidergic perivascular nerves networks in modulating the function, the structure and the proliferative behaviour of vascular smooth muscle cells remains to be clarified.

In the present study, the non-diabetic patients have also had a reduced vascular reactivity to acetylcholine on their "neuropathic" limb, suggestive of a co-existing endothelial defect. This was shown in the previous subchapter to be present in all the diabetic patients with and without neuropathy. Then it was considered to be associated with the metabolic effects and the abnormal oxidative stress induced by diabetes per se, demonstrated as well by animal and in vivo studies (**Pieper et al., 1993; Bucala et al., 1991**).

In non-diabetic patients with predominantly unilateral nerve damage, a reduced response to acetylcholine may be related to a direct impairment of the endothelial function associated with neuropathy or may be secondary to a defect introduced by neuropathy at smooth muscle level.

In an animal study, endothelium-dependent relaxant responses to acetylcholine and substance P were found to be attenuated in the central ear artery of the rabbit with

acrylamide-induced neuropathy, raising also the possibility of the endothelial cell damage as a primary effect or more likely as a secondary consequence of smooth muscle defect associated to perivascular nerve damage (**Maynard et al., 1991**). After experimental sympathetic and sensory denervation of the rabbit ear artery, endothelium-dependent relaxation responses to methacholine were significantly depressed. However the reduction in response was not found to be related to an impairment of smooth muscle function (**Burnstock, 1993**) suggesting that the nerve defect can influence directly the function of the endothelium .

The reduction in the endothelium-dependent vasodilatation to acetylcholine in the present study, could be interpreted as secondary to a defective, non-responsive smooth muscle (where the abnormality introduced by neuropathy might have a specific effect), which does not react adequately to the signals transmitted by the endothelium when triggered with acetylcholine.

To support this hypothesis, there are studies showing that endothelial cells themselves are producing vasodilator neuropeptides (SP, ACh, Ag2, histamine and ATP) independent of their perivascular innervation (**Parnavelas et al., 1985**) and furthermore denervation of the hindlimb vasculature of SP-containing nerves by capsaicin has been shown not to have effect on endothelial release of SP (**Burnstock and Ralevic, 1994**). Consequently it could be argued that the reduction in the endothelium-dependent vasodilatation is unlikely to be a direct consequence of neuropathy, but it is more likely a defective smooth muscle response to vasodilators of both endothelial or exogenous origin.

Therefore it seems that neuropathy has an effect on the endothelial function; whether this effect is primary or secondary to the smooth muscle defect has not yet been established and needs further investigation.

However it is interesting to point out that in the previous subchapter, the diabetic neuropathic group had the smallest (some patients had completely flat traces) range of response to acetylcholine when compared to all the other diabetic groups. In the view of the present study, this may be interpreted as an additive effect introduced by neuropathy to the effect introduced by diabetes on the endothelial function.

In conclusion, the patients with predominantly unilateral nerve damage demonstrated a neuropathy which was similar to that seen in diabetic patients, with damage to large and small fibre function, which resulted in an insensitive foot. They

developed neuropathic ulceration over the sites of high pressure, which proved very slow to heal and became recurrent. The ulceration itself exhibited abundant callus formation which needed to be regularly removed, a feature common in the diabetic neuropathic foot ulcer, and the neuropathic limb was more pigmented than the contralateral side. Paradoxically there was a trend to lower skin temperature on the dorsum of the foot in the "neuropathic" limb although not statistically significant. This raised the question of a decrease in skin blood flow on the dorsum of the foot due to blood being diverted through the arteriovenous anastomoses with a consequent "steal" effect, although previous studies have not confirmed this hypothesis (**Flynn et al., 1988**), or due to the presence of abnormal vascular reactivity as suggested by the present study. Although higher than in the "neuropathic" limb, the range of responses to acetylcholine and SNP in the "control" limbs of non-diabetic patients with predominantly unilateral nerve damage has been found to be smaller than the range of vasodilatatory responses in the non-diabetic controls from the previous subchapter. This might be related to the fact that the so-called "control" limbs had also a degree of neuropathy depending on the level of the nerve damage origin.

With the limitation that the nerve damage is very seldom purely unilateral, these "traumatic" neuropathy patients made an acceptable model for measuring the skin blood flow responses in a neuropathic limb (free from a diabetic "microangiopathy") which suffered recurrent ulceration, thus allowing a parallel to be made with the ulcerated neuropathic foot.

In the present study the very abnormal vascular responses found in the predominantly unilateral neuropathic foot seem to mirror the results of the previous subchapter which showed a reduced smooth muscle reactivity to be associated with diabetic neuropathy.

Conclusion

The abnormal vascular responses seen in the diabetic neuropathic foot, specifically the abnormal vasodilatation to SNP and hence a defective smooth muscle function, may be reproduced by a peripheral neuropathy alone. Furthermore the nerve damage is likely to have an additive effect on the endothelial dysfunction induced by diabetes. The extent to which vascular denervation may precipitate complications of the neuropathic limb, now needs further investigation.

Chapter 8. GENERAL DISCUSSIONS

8.1 Summary of discussions

The pathogenesis of plantar ulceration is not fully understood in the diabetic foot of either neuropathic or neuro-ischaemic origin. A multitude of factors have been implicated in the mechanism of ulcer formation, such as peripheral neuropathy leading to an insensitive foot prone to trauma, peripheral vascular disease and soft tissue abnormalities such as limited joint mobility and increased callus formation, itself leading to high foot pressures. The neuropathic foot has been studied extensively with regard to these factors, whereas such data is not available for the neuro-ischaemic foot. The main purpose of this thesis was to research the fundamental mechanisms of plantar ulcer formation by comparing the foot pressures measured in neuropathic patients to those in neuro-ischaemic patients.

Neuropathic patients, who ulcerate predominantly on the plantar surface, have raised plantar pressures in the presence of callus which is a factor considered to play a role in increasing further the pressures. These elevated levels of pressure may lead to micro-damage of the foot soft tissues and the process of soft tissue repair requires intact neuro-vascular responses of the microcirculation. Although it is accepted that the neuropathic foot is characterised by hyperperfusion due to arterio-venous shunts in the presence of diabetic peripheral neuropathy, the research presented in the thesis has also shown that in the skin of the neuropathic foot the vascular reactivity is impaired due to abnormalities of the microcirculation, both at the endothelial and smooth muscle level.

In comparison to the neuropathic foot, the findings of the thesis have shown that the neuro-ischaemic foot, which tends not to ulcerate on the plantar surface, but predominantly on the margins of the foot, has plantar pressures similar to, if not higher than the neuropathic foot. Furthermore callus has been shown to be a feature of the neuropathic foot, but it is known to be uncharacteristic of the neuro-ischaemic foot **(Foster et al., 1997)**.

As the foot ulcers occur at the shoe-foot interface, the research carried out in the thesis has developed a methodology of in-shoe pressures measurement for clinical use. The establishment of this methodology has also enabled supportive studies to be carried out monitoring therapeutic and preventative methods employed to reduce high foot pressures, such as callus removal and prescription shoewear. These studies can also

provide some information regarding the rate of callus formation. Likewise the assessment of prescription shoewear efficacy in pressure reduction has supported the need for objective measurement of foot pressures.

The results of the thesis support the multifactorial theory of pathogenesis of neuropathic foot ulceration, showing that high foot pressures, peripheral neuropathy, abnormal microvascular reactivity, callus formation and unsuitable footwear are important risk factors which need to act concomitantly or in addition to each other in order to lead to ulceration. In the neuro-ischaemic foot, the absence of one of these factors, such as callus or the presence of another factor, such as poor blood supply characteristic for the ischaemic patients, can paradoxically 'protect' from ulceration on the plantar surface.

8.1.1 Foot pressure measurement in neuropathic and neuro-ischaemic feet

Neuropathic ulceration has been studied extensively and plantar pressures have been found to play an important role in its multifactorial aetiology. In diabetic neuro-ischaemic patients, who also have a high risk of ulceration, firstly, because of their peripheral vascular disease and secondly, because most of them have an underlying degree of neuropathy, there have been no similar studies assessing the foot pressures. To the best of our knowledge, this thesis contains the first study measuring plantar pressures in neuro-ischaemic patients.

In neuropathic patients the majority of foot ulcers develop on the plantar surface under areas of high pressure, such as bony deformity or metatarsal heads.

Neuro-ischaemic patients tend not to develop ulcers on the plantar surface but more on the sides of the foot or on the upper margin or in between the toes. In the present study, although the neuro-ischaemic patients did not have a history of plantar ulceration, their vertical plantar pressures were consistently high, even higher than the neuropathic patients who tend to develop ulcers underneath the foot. The neuro-ischaemic patients taken into the study had also a similar degree of neuropathy to the neuropathic patients; their vibration perception threshold was above 25Volts, which is considered to be the threshold of risk for ulceration. However this was not associated with plantar ulceration, indicating different mechanisms of ulcer formation between ischaemic and neuropathic diabetic patients.

The neuro-ischaemic patients had a pattern of pressure loading suggestive of a constant, normal gait. This pattern of gait was similar to the diabetic controls and non-diabetic controls, but the latter had lower foot pressures. However the neuropathic patients, who, had also high pressures, showed a pressure loading pattern suggestive of a variable gait.

It is possible that the same mechanism of ulcer formation does take place in both the neuropathic and neuro-ischaemic foot, but ulcers do not occur in the absence of certain factors associated with ulceration, such as a variable pressure loading pattern or callus, which has been noted to be frequently found in the areas of high pressure of the neuropathic foot, but it is less prominent, if not absent in the neuro- ischaemic foot. Therefore the absence of these factors in the ischaemic foot may have protective effects.

The limitations of this study are that these were measurements of vertical forces only, but the shear stresses have not been assessed in either neuropathic or neuro-ischaemic foot due to the absence of a clinically available shear transducer. Shear forces developed at the shoe-foot interface, in the absence of reliable evidence, have been implicated in the aetiology of foot ulceration in neuro-ischaemic patients.

Another essential factor in the pathogenesis of foot ulceration, which may be possibly reduced in the neuro-ischaemic foot, is the level of activity. Neuro-ischaemic patients may claudicate and simply walk less in comparison to the neuropathic patients with insensitive feet.

8.1.2 Microcirculation neuro-vascular reactivity in the neuropathic foot

Plantar pressures act on the underlying soft tissues of the foot interacting with their properties in the mechanism of ulcer formation. It is already accepted that soft tissue abnormalities, such as limited joint mobility can be related to microcirculatory defects. The mechanisms involved in repair of micro-damage of the soft tissue also require intact neuro-vascular reflexes. In this thesis it was attempted to elucidate another possible factor implicated in the foot ulceration pathogenesis, the neuro-vascular reactivity of the skin microcirculation. Microcirculatory abnormalities have been studied with particular regard to neuropathy, whether or not diabetic.

In this thesis the initial study of skin neuro-vascular reactivity has shown that endothelium-dependent vasodilatation induced by acetylcholine in the foot was impaired in all the patients with diabetes mellitus, whereas the smooth muscle response to sodium nitroprusside was severely blunted only in patients with diabetic neuropathy. This was true for both the difference and the ratio of peak to basal blood flow. A second study, this time carried out in neuropathic patients with a history of ulceration but without diabetes, has shown that the abnormal vascular responses seen in the diabetic neuropathic foot, specifically the abnormal vasodilatation to SNP and hence a defective smooth muscle function, may be reproduced by a peripheral neuropathy alone. The nerve damage is likely to have an additive effect on the endothelial dysfunction already induced by diabetes. Recently Veves et al. **(1998)** have reported work which suggests that further reduced responses are found in neuro-ischaemic patients when compared to neuropathic patients. The extent to which vascular denervation may precipitate complications of the neuropathic limb however needs further investigation.

8.1.3 Effect of callus formation and removal on plantar pressures

In the neuropathic foot, callus has been shown to act as a foreign body and to increase further the plantar pressures. The neuropathic feet with a good blood supply develop 'hot' spots and callus build-up in response to continuous repetitive pressure. The neuro-ischaemic feet do not build-up so much callus, possibly because of the poor blood supply. Therefore the findings of high pressure in neuro-ischaemic patients seem not to be related to the callus formation, but they may be possibly related to an atrophic soft tissue with altered cushioning properties.

In this thesis the effect of callus removal in reducing plantar pressures in the neuropathic foot has been assessed and then for the first time, to our best knowledge, the rate of callus formation has been followed-up in relation to the increase in plantar pressures in a pilot study.

Callus removal lead to a significant reduction in plantar pressures of 32% in patients at their first ever visit to chiropodist, of 30% in patients requiring regular chiropody at 6-8 weeks time interval and of 31% in those coming more frequently at 3-4 weeks interval. The results obtained suggest either that the chiropodial technique of callus removal has a similar effect on plantar pressures at different time-intervals, being

able to reduce the pressures overall with approximately 30%, or that the rate of callus formation tends to reach a plateau after an initial period of pressure elevation.

These findings have shown that the F-Scan methodology can provide the facility to follow-up the callus formation until it reaches the upper limits of acceptable pressure and requires removal. This might prove of benefit for reducing the costs of foot care by reducing the frequency of chiropodial treatment and making it more cost-effective.

8.1.4 Effect of prescription shoewear on plantar pressures

Whereas callus removal is a short term measure of foot pressure reduction, a method for a long term reduction of foot pressures has been also assessed in this thesis, a new type of insert for prescription shoewear, the custom-moulded EVA insert.

The F-Scan technology has allowed the assessment of custom-moulded EVA insert fitted in bespoke shoes. This study has shown that made-to-measure prescription shoes fitted with custom-moulded EVA inserts, were found to be the most efficient in reducing high plantar pressures developed in the neuropathic foot with a history of ulceration. EVA inserts in bespoke shoes proved to be better than High Street shoes and also better than trainers. When the plantar pressures were measured initially in newly fitted prescription shoes with custom-moulded EVA inserts and then the measurement was repeated a few weeks later, the latter showed even lower pressures than the initial one suggesting a continuation of the moulding process with wearing. Furthermore when new and previously issued prescription shoes, which have been worn for a longer period of time, were compared, the latter also showed lower pressures leading to the clinical recommendation that our new prescription shoes with custom-moulded EVA inserts should be 'broken in' gradually.

The greatest percentage fall in pressure with prescription shoes with custom-moulded EVA inserts was found in the patients with the highest plantar pressures, suggesting that they benefit the most from this footwear. As high plantar pressures are recognised to be an important aetiological factor in foot ulcer formation it may be of benefit to set up a screening programme for high foot pressures in the diabetic population. Then in order to prevent ulceration, prescription footwear would be recommended for those diabetic patients detected to have high foot pressures, even in the absence of a history of ulceration, particularly for pure neuropathic patients.

Although trainers were found to induce a smaller reduction in pressure than bespoke shoes with custom-moulded EVA inserts, trainers can provide a useful and educative alternative to High Street shoes. Furthermore trainers proved to have a comparable effect, if not a beneficial effect over stock shoes fitted with flat Poron inserts. This highlights the potential role which trainers may have in prevention of ulceration in the early stages of the foot at risk, when is not deformed and has good proprioceptive sensation. Trainers also have the advantage of being generally less expensive than the stock prescription shoes. They are also easily accessible and a high specification pair of trainers is often more cosmetically acceptable. At this stage the protection can be achieved without the expenses implied by individually designed inserts and bespoke shoes such as our prescription shoes with custom-moulded inserts. They are nevertheless vital for patients with recurrent ulceration and feet at risk, who need an individualised choice of cushioning materials and insert design.

This study has confirmed the feasibility of quantitative assessment of foot pressure changes with different types of footwear on a cross-sectional basis. These findings stress the usefulness of modern techniques, such as F-Scan, as a visual and quantitative aide in footwear assessment, to be used for the design of moulded and orthopaedic shoes. These techniques should now be used to address the problems of design and manufacture of inserts and prescription shoes for the diabetic foot.

8.1.5 Development of the F-Scan methodology for dynamic foot pressure measurement

Crucial to this thesis it has been the development of in-shoe dynamic foot pressure measurement. A methodology for measuring in-shoe foot pressures, which is feasible and adequately reproducible has been developed in this thesis. The two most commonly used methods for in-shoe foot pressure measurement, F-Scan and EMED have both strengths and weaknesses: F-Scan has a better spatial resolution in comparison to EMED, which is more reproducible. With the F-Scan, problems were experienced due to changes in sensitivity leading to a great variability of measurement. Therefore a study was set-up to test the time-dependent behaviour of the F-Scan sensor when a cyclical load was applied with an Instron machine. These trials showed an increase in sensitivity of this FSR insole transducer during loading. The rapid element,

demanded the insole to be conditioned by at least 60 seconds of loading prior to calibration, and that a trial walk be undertaken within a few seconds thereafter. Because of a creep-like element of the response, sensitivity continued to change slowly over several minutes even after the initial rapid rise is finished. This necessitates calibration at frequent intervals.

In this thesis it was the aim to achieve acceptable reproducibility necessary for the study of foot pressures in clinical practice. Therefore a methodology has been developed which takes into account the technical features of the F-Scan equipment in correlation with the clinical conditions in which the tests are performed and the subsequent recommendations for a recording technique have been established:

Recommended recording technique

If a new insole is used, the patient (wearing standard shoes and socks) is asked to walk normally on a flat, even surface for 2 minutes in order to reach a suitable level of "bedding-in"/ sensitivity. If an insole had been used previously, the patient is asked to walk only for 1 minute in order to acclimatise the insole to the in-shoe conditions and the patient's foot temperature is stabilised to the room temperature. Then the insole is calibrated against each individual body weight and then the initial run done immediately. Calibration again at the end of the F-Scan test is recommended to check for major artefacts in insole sensitivity.

It is recommended that an F-Scan test consists of 3 runs. The initial run is a learning one. The next two runs are recorded, i.e. one and a 'back-up'. It is advisable not to record consecutively more than 3 runs in a patient.

However it is not recommended to use an insole for more than 20 runs in total and if tracks are missing persistently on the screen. It would be advisable to keep one insole per patient especially if longitudinal studies are to be done.

In the analysis of pressure, the second step of the second run or the mean of all the steps in a run is advisable in order to standardise the assessment of peak pressures.

The coefficients of variation were calculated when using this technique of foot pressure measurements in non-diabetic controls (10.3%) and diabetic neuropathic patients (18.9%). These agree with other methods of foot pressure measurement variability suggesting that the F-SCAN offers an acceptable reproducibility in assessing the foot pressures during gait.

8.2 Rationale for future studies

Foot pressure measured by analysis of in-shoe dynamic peak pressure using the F-SCAN is now suitable for clinical use and should enable further exploration of the causative factors of foot problems, notably those of diabetic ulceration, in realistic shod conditions.

Thus this methodology could now be used in future studies for detection of a in-shoe foot pressure threshold for ulceration. As high plantar pressures are recognised to be an important aetiological factor in foot ulcer formation it may be of benefit to set up a screening programme for high foot pressures in the diabetic population. This could be part of a wider screening programme for foot ulcer assessing other risk factors involved in the multifactorial aetiology of ulceration: peripheral neuropathy, micro- and macro-vascular disease and other factors such as limited joint mobility, foot deformity, level of activity and type of footwear.

The findings of the research presented in this thesis have also shown that patients with the highest plantar pressures had the greatest percentage fall in pressure when wearing prescription shoes, suggesting that they benefit the most from prescription footwear. Then in order to prevent ulceration, prescription footwear with fitted inserts would be recommended for those diabetic patients detected at screening to have high foot pressures, even in the absence of a history of ulceration. Prescription footwear with custom-moulded inserts proves to be the most efficient in reducing plantar pressures, but is costly. Therefore new technologies such as CADCAM technique need to be developed in order to produce this footwear rapidly, reliably and at a moderate cost.

The research presented in this thesis also highlights the need for longitudinal studies to assess the characteristics of prescription footwear and to correlate these with recurrence of ulceration. The life-time of an insert fitted in prescription shoes is not known and longitudinal studies to define physical and clinical end-points are needed. They could be carried out with the F-Scan technology. The definition of the end-points has to be based on quantitative assessment of the ability of the insole to maintain the redistribution of pressure as well as its usefulness in preventing the recurrence of foot ulcer. It is not known for how long an insole should be used. Whether replacement should depend on simple assessment of its physical state or be related to more scientific pressure measurements to assess its capability to reduce peak pressures and maintain them at a safe level to prevent recurrence of ulceration remains to be studied.

The findings of the study presented in Chapter 6 put into question both the principles and practice of prescribing therapeutic inserts and indicates that considerable value might come from the dynamic measurement of foot pressures inside both prescription footwear and High Street shoes. It is advisable that shoes should be prescribed and fitted in centres which use this equipment to achieve the optimal outcome. This study has also indicated that in certain circumstances there is an increase in foot pressures in patients going from their own shoes to trainers or Poron insoles. Therefore, there is a need for immediate 'on the spot' pressure assessment of the effect of recommended footwear, particularly of stock orthopaedic shoes and insoles in comparison with their own footwear. This stresses the importance of a Shoe Clinic within the Diabetic Foot Centre, which would also be able to develop and produce guidelines to be used in other centres not having the use of pressure measurement equipment.

There has been no previous studies examining the value of certain High-Street shoes and this study has proven that sometimes trainers could be more efficient than certain types of supplied footwear. Therefore there is a need for systematic assessment of High Street shoes and their inserts. There is an array of shoes and inserts available to patients and very little is known of their properties and their ability to redistribute pressure although is has been documented that poor footwear is responsible for foot ulceration **(Edmonds, 1986)**. Some of these inserts may be found to be efficient in redistributing pressures and this information needs to be confirmed with diabetic patients.

Thus the methods described allow investigations of the prescription footwear and High-Street shoes. This will help to improve the advice given to patients about shoes and footwear, which at present is lacking detail of information.

Although the in-shoe measurement of foot pressures needs to be included in a screening programme for foot ulceration, other factors involved in its pathogenesis still ought to be considered in order to have a predictive and preventative tool. There is a need for development of technologies assessing other factors involved in the mechanism of ulcer formation, such as shear forces, and for further studies to measure the shear forces inside the shoe, with special emphasis in the neuro-ischaemic patients who possibly are the most vulnerable to shear stress.

The pathogenesis of the neuro-ischaemic ulcer has been studied critically in this thesis: elevated plantar pressures have been found, but in the absence of callus

formation and plantar ulceration, with a trend to ulcer formation on the margins of the foot. The whole issue of ulceration in neuro-ischaemic patients raises new question for future research as regards the time characterisation of pressures distribution inside the shoe, the size and role of shear stresses in foot ulceration, and the role of soft tissue characteristics in the aetiology of diabetic foot ulcer.

A soft tissue abnormality playing a role in ulceration is callus formation associated in neuropathic patients with increased plantar pressures. Using the F-Scan technology, longitudinal studies of plantar pressure in correlation with chiropodial follow-up are needed now in a larger number of patients. The measurement of foot pressures before and after chiropody may prove to be a useful 'on the spot' assessment of the efficacy of the callus removal. Longitudinal studies as demonstrated by diagrams drawn for our follow-up case studies (Chapter 5) could be included in the notes of the patients coming to the Diabetic Foot Clinic in order to provide the necessary documentation regarding the change in plantar pressure before and after chiropody at each visit. These observations of plantar pressures are of interest, but further close follow-up of a larger number of patients is required. Weekly measurement of plantar pressures is needed to assess the rate of callus formation and to define, on a larger number of patients, the threshold of pressure for removal of callus and also to evaluate alternatives to debridement e.g. use of emollients in order to keep the diabetic foot free from ulceration.

Clinical ulceration and soft tissue necrosis is ultimately due to microcirculatory failure in a background of neuropathy together with macrovascular disease in certain cases. The perivascular nerves, the endothelium and the smooth muscle create a complex system in which neuro-vascular abnormalities can have an effect on the tissue repair process. The findings presented in the Chapter 7 indicated that vascular endothelial responses are blunted in diabetes, while neuropathy might affect specifically the NO dependent smooth muscle reactivity. These results highlight the need for further studies to explore these different pathways using other vasodilator or vasoconstrictor neurotransmitters, in order to establish more precisely the site where neuropathy affects this complex system. Also these future studies are needed to elucidate the underlying mechanisms of these observations and their relationship with the susceptibility to foot ulceration.

8.3 Main conclusions

This thesis has made novel observations in both the neuropathic and neuro-ischaemic foot.

In conclusion, this thesis has shown for the first time that the neuro-ischaemic patients had higher plantar pressures than the neuropathic patients, and also higher than diabetic control subjects and non-diabetic control subjects. This is of interest, knowing that the neuro-ischaemic foot is not characterised by excessive callus formation or by plantar ulceration in contrast to the neuropathic foot.

However the pattern of pressure loading in neuro-ischaemic patients was similar to the pattern of pressure loading of the controls groups, whereas the neuropathic patients demonstrated a variable pattern of pressure loading suggestive of a variable gait. These comparative observations may have relevance to the mechanism of ulceration in the diabetic (neuro-ischaemic and neuropathic) foot.

These findings support the multifactorial theory of foot ulceration. Furthermore this thesis has highlighted two other potential factors, the endothelial and smooth muscle of the skin microcirculation, whose function is decreased in patients with neuropathy and a history of ulceration. When assessing the neuro-vascular reactivity of the skin of the foot, the endothelial and smooth muscle function were found to be both reduced in diabetic neuropathic patients, as well as in neuropathic patients without diabetes, but also with a history of foot ulceration, suggesting that neuropathy seems to be associated to microcirculatory defects, which may decrease the ability of the soft tissue of the foot to defend itself against the noxious stimuli, such as trauma or high foot pressures.

The role of increased foot pressures in the aetiology of ulceration has been extensively assessed by firstly developing and validating a methodology for measurement of in-shoe foot pressures, which achieved acceptable reproducibility. Foot pressure measured by analysis of in-shoe dynamic peak pressure using the F-SCAN is now feasible and adequately reproducible and should enable further exploration of the causative factors of foot problems, notably those of diabetic ulceration, in realistic shod conditions.

The established F-Scan method has been used to assess the effect of different methods used to reduce the plantar pressures. Callus removal and prescription shoewear, two measures used in the Diabetic Foot Clinic for the treatment and prevention of foot ulceration, have been evaluated regarding their effect on foot pressures.

This thesis has shown that chiropody is an essential therapeutic tool, callus removal leading to a significant reduction in plantar pressures. However independent of the time interval between treatments and the rate of callus formation, the actual chiropodial technique of callus removal has an overall decreasing effect on the plantar pressures around 30%. The rate of callus formation varies in different individuals probably related with their level of activity and mobility. By assessing the effect of chiropodial treatment on foot pressures further information was obtained regarding a factor involved in the mechanism of ulceration, namely on callus and its rate of formation. The research presented in the thesis has demonstrated the measurement of plantar pressures to be a functional and objective indicator valuable in the assessment of chiropodial treatment.

This thesis has also assessed measures used in the prevention of foot ulceration, such as prescription footwear, by comparing the effect of different types of footwear on foot pressures. Made-to-measure prescription shoes fitted with a new type of insert, custom-moulded EVA insert, which are usually prescribed to prevent recurrence of foot ulceration in both neuropathic and neuro-ischaemic patients, have been the most efficient in reducing high plantar pressures. They proved to be better than High Street shoes and also better than trainers. However when newly fitted prescription shoes with custom-moulded EVA inserts were assessed on follow-up, even lower pressures were found than at the baseline, suggesting a continuation of the moulding process with wearing.

Therefore these findings of the thesis suggest that measures employed in the prevention of foot ulceration, such as prescription footwear need to be assessed and developed by using objective measurements, such as dynamic foot pressure measurement inside the shoe.

APPENDIX I: List of publications

Pitei DL, Watkins PJ, Stevens MJ, Edmonds ME. The value of the Neurometer in assessing diabetic neuropathy by measurement of the current perception threshold. Diabet-Med. 1994; 11: 872-6.

Pitei DL, Ison K, Edmonds ME, Lord M. Time-dependent behaviour of a force-sensitive resistor plantar pressure measurement insole. Proc-Inst-Mech-Eng (H). 1996; 210: 121-5.

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332